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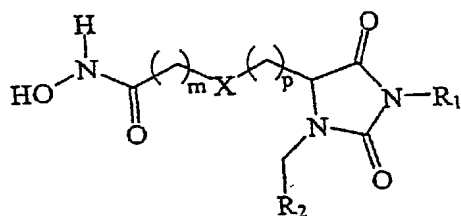
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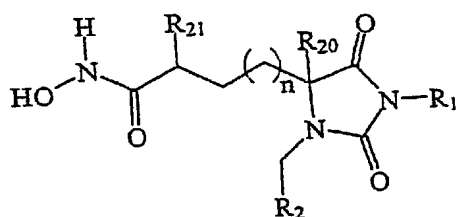
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(54) Title: HYDANTOIN C-PROTEINASE INHIBITORS



(Ia)



(Ia')

(57) Abstract: The present invention relates to a novel class of N,N'-di substituted hydantoin hydroxamates (Ia) or (Ia') capable of inhibiting C-proteinase, and to their use to regulate, modulate, and/or inhibit abnormal collagen formation as a therapeutic approach towards the treatment of fibrotic disorders.



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HYDANTOIN C-PROTEINASE INHIBITORS

5 1. FIELD OF THE INVENTION

The present invention relates to a novel class of organic molecules capable of inhibiting the enzyme C-proteinase, pharmaceutical compositions comprising these C-proteinase inhibitory compounds, and methods of using these compounds and
10 compositions to regulate, modulate, and/or inhibit collagen production and/or maturation as a therapeutic approach to the treatment or prevention of myriad diseases related to, or associated with, unregulated collagen production.

15 2. BACKGROUND OF THE INVENTION

Collagen Structure. At present, nineteen different types of collagens have been identified. These collagens, which include fibrillar collagen types I, II, and III, are
20 synthesized as procollagen precursor molecules which contain peptide extensions at both their amino- and carboxy-termini. These peptide extensions, referred to as "pro-regions," are designated as N- and C-propeptides, respectively.

The pro-regions are typically cleaved upon secretion of
25 the procollagen triple helical precursor molecule from the cell to yield a mature triple helical collagen molecule. Upon cleavage, the "mature" collagen molecule is capable of association, for example, into highly structured collagen fibers. See e.g., Fessler and Fessler, 1978, *Annu. Rev. Biochem.* 47:129-162; Bornstein and Traub, 1979, in: *The Proteins* (eds. Neurath, H. and Hill, R.H.), Academic Press,
30

New York, pp. 412-632; Kivirikko et al., 1984, in: *Extracellular Matrix Biochemistry* (eds. Piez, K.A. and Reddi, A.H.), Elsevier Science Publishing Co., Inc., New York, pp. 83-118; Prockop and Kivirikko, 1984, *N. Engl. J. Med.*

- 5 311:376-383; Kuhn, 1987, in: *Structure and Function of Collagen Types* (eds. Mayne, R. and Burgeson, R.E.), Academic Press, Inc., Orlando, Florida, pp. 1-42.

Diseases Associated With The Abnormal Production of

- 10 ***Collagen.*** A variety of critical diseases have been linked to inappropriate or unregulated collagen production and/or maturation. These diseases include pathological fibrosis or scarring (including endocardial sclerosis), idiopathic interstitial fibrosis, interstitial pulmonary fibrosis,
- 15 perimuscular fibrosis, Symmers' fibrosis, pericentral fibrosis, hepatitis, dermatofibroma, biliary cirrhosis, alcoholic cirrhosis, acute pulmonary fibrosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney fibrosis/glomerulonephritis, kidney fibrosis/diabetic
- 20 nephropathy, scleroderma/systemic, scleroderma/local, keloids, hypertrophic scars, severe joint adhesions/arthritis, myelofibrosis, corneal scarring, cystic fibrosis, muscular dystrophy (Duchenne's), cardiac fibrosis, macular fibrosis/retinal separation, esophageal stricture, and
- 25 Peyronie's disease, etc. Further fibrotic disorders may be induced or initiated by various conditions or events, such as surgery, including scar revision/plastic surgeries, glaucoma, cataract fibrosis, corneal scarring, joint adhesions, graft vs. host disease, tendon surgery, nerve entrapment,
- 30 Dupuytren's contracture, OB/GYN adhesions/fibrosis, pelvic adhesions, peridural fibrosis, restenosis, etc. One strategy for the treatment of these diseases is to inhibit the pathological overproduction of collagen. Thus, identification

and isolation of molecules which control, inhibit, and/or modulate the production of collagen are of major medical interest.

5 ***Relationship Between Collagen Formation and C-Proteinase.***

Recent evidence suggests that C-proteinase is the essential key enzyme that catalyzes the cleavage of the C-propeptide of, for example, fibrillar collagens, including type I, type II, and type III collagen. See e.g. Prockep et al., 1998, *Matrix Biol.* 16:399-408; Lee et al., 1997, *J. Biol. Chem.* 272:19059-19066; Suzuk et al., 1996, *Development* 122:3587-3595.

C-proteinase was first observed in the culture media of human and mouse fibroblasts (Goldberg et al., 1975, *Cell* 4:45-50; Kessler and Goldberg, 1978, *Anal. Biochem.* 86:463-469), and chick tendon fibroblasts (Duskin et al., 1978, *Arch. Biochem. Biophys.* 185:326-332; Leung et al., 1979, *J. Biol. Chem.* 254:224-232). An acidic proteinase which removes the C-terminal propeptides from type I procollagen has also been identified. Davidson et al., 1979, *Eur. J. Biochem.* 100:551.

A partially purified protein having C-proteinase activity was obtained from chick calvaria in 1982. Njieha et al., 1982, *Biochemistry* 23:757-764. In 1985, chicken C-proteinase was isolated, purified, and characterized from conditioned media of chick embryo tendons. Hojima et al., 1985, *J. Biol. Chem.* 260:15996-16003. Murine C-proteinase has been subsequently purified from media of cultured mouse fibroblasts. Kessler et al., 1986, *Collagen Relat. Res.* 6:249-266; Kessler and Adar, 1989, *Eur. J. Biochem.* 186:115-121. Finally, the cDNA encoding human C-proteinase has been identified (see, e.g., Takahara et al., 1994, *J. Biol. Chem.* 269:26280-26285; Li et al., 1996, *Proc. Natl.*

Acad. Sci. USA 93:5127-5130; Kessler et al., 1996, *Science* 271:360-362.

C-Proteinase Inhibitors. Experiments conducted with
5 purified forms of chick and mouse C-proteinases indicate that
C-proteinase is instrumental in the formation of functional
collagen fibers. Fertala et al., 1994, *J. Biol. Chem.*
269:11584. As a consequence of its critical role in collagen
production and maturation, scientists have sought to identify
10 compounds that inhibit C-proteinase. See e.g., Hojima et al.,
supra. Compounds identified to date include metal chelators
(e.g., EDTA, phenanthroline, EGTA, basic amino acids (e.g.,
lysine and arginine), peptides (e.g., chymostatin, pepstatin
A, and concanavalin A), proteins (e.g., α_2 -macroglobulin,
15 ovostatin, and fetal bovine serum), metals ions (e.g., Zn^{2+} ,
 Cu^{2+} , and Cd^{2+}), reducing agents (e.g., dithiothreitol),
detergents (e.g., sodium dodecyl sulfate (SDS)), and certain
salts and buffers (e.g., phosphate, ammonium sulfate, sodium
chloride and tris hydrochloride). In contrast, microbial
20 inhibitors such as leupeptin, phosphoramidon, antipain,
bestatin, elastinal, and amastatin are considered to have weak
or no effect on the activity of C-proteinase. For references
discussing the various C-proteinase inhibitors identified to
date, see Leung et al., *supra*; Ryh nen et al., 1982, *Arch.*
25 *Biochem. Biophys.* 215:230-236; WO97/05865; and the references
cited therein.

Matrix Metalloproteinase Hydroxamic Acid Inhibitors.

C-proteinase belongs to the matrix metalloproteinase (MMP)
30 superfamily of zinc endopeptidases which are involved in
tissue remodeling. Members of the MMP family include MMP-1
(human collagenase), MMP-2 (gelatinase), and MMP-9 (human
gelatinase B). See e.g. WO98/34918; Krumme et al., 1998, *FEBS*

Lett. 436:209-212. The MMPs are characterized by an active site zinc ion that plays an essential role in the enzymatic activity of MMPs. Rational drug discovery efforts, involving the inhibition of MMPs, have focused on inhibitor classes that contain a functional group that can coordinate the zinc ion and thereby inactivate the target MMP. See e.g. Krumme et al., *supra*. One such inhibitor class are hydroxamic acids. As revealed by the x-ray crystal structure determination of hydroxamic acid:MMP cocrystals, the hydroxamic acid coordinates the active site zinc in a bidentate manner via the hydroxyl and carbonyl oxygens of the hydroxamic group. See Grams et al., 1995, *Biochem.* 34:14012-14020; Bode et al., 1994, *EMBO J.*, 13:1263-1269. Despite their potent affinity as zinc coordinators, hydroxamic acids demonstrate a considerable degree of specificity within the MMP family. Thus a potent inhibitor of MMP-1 (human collagenase) may have only minimal potency against another MMP such as C-proteinase. Thus the development of potent hydroxamic acid inhibitors against a particular MMP requires considerable research effort and experimentation.

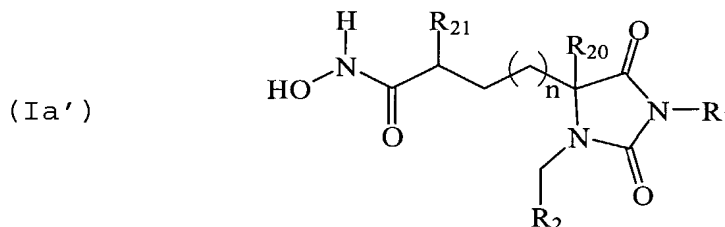
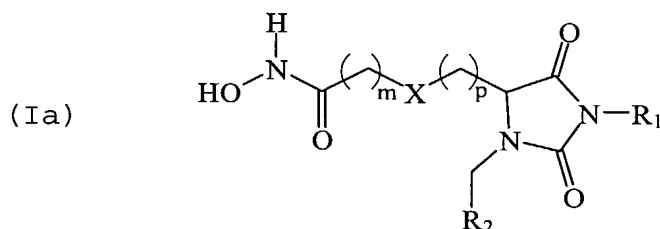
Development Of Compounds To Inhibit C-Proteinase

Activity. In view of its essential role in the formation and maturation of collagen, C-proteinase provides an ideal therapeutic target for the treatment or prevention of disorders related to, or associated with, unregulated collagen production or maturation. Accordingly, there remains a need in the art for compounds that are specific and potent inhibitors of C-proteinase, especially C-proteinase inhibitory compounds which provide clinically relevant benefits in the treatment or prevention of diseases associated with unregulated collagen production and/or maturation.

3. SUMMARY OF THE INVENTION

In one aspect, the present invention provides a novel class of organic molecules that are potent and/or selective inhibitors of C-proteinase. As a consequence of this activity, the compounds of the invention are capable of modulating, regulating, or inhibiting collagen production or maturation by affecting C-proteinase activity.

The compounds of the invention are generally substituted hydantoin compounds according to structural formulae (Ia) and (Ia'):



or pharmaceutically acceptable salts thereof, wherein:

m is an integer from 0 to 3 when X is NR₁₉, or an integer from 1 to 3 when X is S or O;

p is an integer from 1 to 4 when X is NR₁₉, or an integer from 1 to 3 when X is S or O;

n is an integer from 1 to 3;

X is NR₁₉, S or O;

R₁₉ is selected from the group consisting of hydrogen, (C₁-C₅) alkyl, and (C₁-C₅) substituted alkyl;

R₁ and R₂ are each independently selected from the group consisting of (C₁-C₁₀) alkyl, (C₁-C₁₀) substituted alkyl, (C₃-C₁₀)

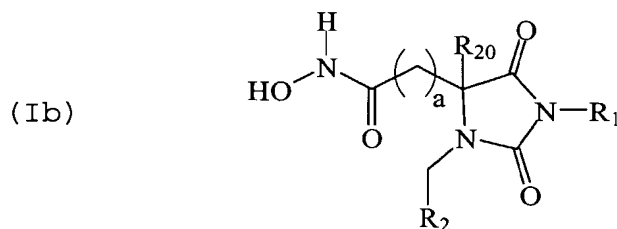
alkenyl, (C₃-C₁₀) substituted alkenyl, (C₃-C₁₀) alkynyl, (C₃-C₁₀) substituted alkynyl, (C₃-C₂₀) cycloalkyl, (C₃-C₂₀) substituted cycloalkyl, 3-20 membered heterocycloalkyl, 3-20 membered substituted heterocycloalkyl, (C₅-C₂₀) aryl, (C₅-C₂₀) aryl independently substituted with one or more Y¹, alkaryl, alkaryl independently substituted with one or more Y¹, 5-20 membered heteroaryl, 5-20 membered heteroaryl independently substituted with one or more Y¹, 6-26 membered alk-heteroaryl, and 6-26 membered alk-heteroaryl independently substituted with one or more Y¹;

R₂₀ and R₂₁ are each independently selected from the group consisting of hydrogen, (C₁-C₁₀) alkyl, (C₆-C₂₆) alkaryl, and 6-26 membered alk-heteroaryl; and

each Y¹ is independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃, and -heteroaryl; where each R is independently selected from the group consisting of hydrogen, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl, and 6-26-membered alk-heteroaryl;

with the proviso that the sum of **m** and **p** is 1, 2, 3, or 4.

In a preferred embodiment, the compounds of the invention are generally substituted hydantoin compounds having the structural formula (Ib):



or pharmaceutically acceptable salts thereof, wherein:

5 **a** is an integer from 2 to 5; and

R_1 , R_2 , and R_{20} are as defined for formula (Ia).

In another aspect, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of one or more of the above-described compounds and a pharmaceutically acceptable carrier, diluent, or excipient. Such a composition can be used in the methods of the invention to inhibit, regulate, or modulate the production or maturation of collagen by inhibiting C-proteinase activity, and to treat or prevent a variety of collagen-related disorders.

In yet another aspect, the invention provides methods of inhibiting C-proteinase activity. The method involves contacting the enzyme C-proteinase, or an active fragment or derivative thereof, with an amount of a compound or composition according to the invention effective to block collagen production. Methods of inhibiting C-proteinase *in vivo* can be used to inhibit, regulate, or modulate collagen production or maturation as a therapeutic approach towards the treatment or prevention of disorders related to, or associated with, unregulated collagen production or maturation.

In a final aspect, the present invention provides methods for the treatment or prevention of disorders related to, or associated with, inappropriate or unregulated collagen production or maturation. The method involves administering to an animal subject, including a human, an amount of a

compound according to the invention, or a pharmaceutical composition thereof, effective to treat or prevent the particular collagen-related disorder.

Disorders which can be treated or prevented according to the methods of the invention include, but are not limited to, rheumatoid arthritis, scleroderma, pathological fibrosis, or scarring.

4. DEFINITIONS

As used herein, the following terms shall have the following meanings:

"C-proteinase": refers to an enzyme capable of processing collagen molecules or derivatives, or fragments or precursors of collagen molecules, derivatives, or fragments, by cleaving the amino acid sequence -Ala↓Asp-Asp-, -Gly↓Asp-Glu- and/or -Ala↓Asp-Gln- at the position marked with "↓". The term "C-proteinase" includes human C-proteinase as well as derivatives, analogs, fragments, and variants thereof capable of processing collagen molecules as described above.

"Alkyl": refers to a saturated branched, straight chain or cyclic hydrocarbon radical. Typical alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, t-butyl, cyclobutyl, pentyl, isopentyl, cyclopentyl, hexyl, and cyclohexyl groups and the like. In preferred embodiments, the alkyl groups are (C₁-C₈) alkyl, more preferably (C₁-C₆) alkyl, and most preferably (C₁-C₃) alkyl.

"Substituted Alkyl": refers to an alkyl radical that has been substituted with one or more Q. Typical substituents Q include, but are not limited to, -X, -OR, -NRR, -N₃, -CN, and

-CX₃; where each R is independently hydrogen, alkyl, or substituted alkyl, and X is halogen.

"Alkenyl": refers to an unsaturated branched, straight
5 chain, or cyclic hydrocarbon radical having at least one
carbon-carbon double bond. The radical may be in either the
cis or *trans* conformation about the double bond(s). Typical
alkenyl groups include, but are not limited to, ethenyl,
propenyl, isopropenyl, isopropylidene, butenyl, butenylidene,
10 isobutenyl, *tert*-butenyl, cyclobutenyl, pentenyl, isopentenyl,
cyclopentenyl, hexenyl, and cyclohexenyl groups, and the like.
In preferred embodiments, the alkenyl group is (C₂-C₈) alkenyl,
more preferably (C₂-C₆) alkenyl and most preferably (C₃-C₄)
alkenyl.

15
"Substituted Alkenyl": refers to an alkenyl radical that
has been substituted with one or more Q. Typical Q include,
but are not limited to, -X, -OR, -NRR, -N₃, -CN, and -CX₃;
where each R is independently hydrogen, alkyl, or substituted
20 alkyl, and X is halogen.

"Alkynyl": refers to an unsaturated branched,
straight-chain or cyclic alkyl group having at least one
carbon-carbon triple bond. Typical alkynyl groups include,
25 but are not limited to, ethynyl; propynyls such as
prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as
but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the
like. In preferred embodiments, the alkynyl group is (C₃-C₆)
alkynyl.

30
"Substituted Alkynyl": refers to an alkynyl radical that
has been substituted with one or more Q. Typical Q include,
but are not limited to, -X, -OR, -NRR, -N₃, -CN, and -CX₃;

where each R is independently hydrogen, alkyl, or substituted alkyl, and X is halogen.

"Cycloalkyl": refers to a cyclic or polycyclic saturated or unsaturated hydrocarbon radical. Typical cycloalkyl groups include, but are not limited to, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, and higher cycloalkyls, adamantyl, cubanyl, prismanyl, and higher polycyclicalkyls, etc. In preferred embodiments, the cycloalkyl is (C₃-C₁₀) cycloalkyl. Particularly preferred cycloalkyls are cyclohexanyl and adamantyl.

"Substituted Cycloalkyl": refers to a cycloalkyl or radical wherein one or more hydrogen atoms are each independently replaced with another substituent. Typical substituents include, but are not limited to, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, -OR, -SR, -NRR, -CN, -NO₂, -C(O)R, -C(O)OR, -C(O)NRR, -C(NRR)=NR, -C(O)NROR, -C(NRR)=NOR, -NR-C(O)R, -tetrazol-5-yl, -NR-SO₂-R, -NR-C(O)-NRR, -NR-C(O)-OR, -halogen, and -trihalomethyl; where each R is independently -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, and (C₆-C₂₆) alkaryl as defined herein.

"Heterocycloalkyl": refers to a cycloalkyl moiety wherein one of the ring carbon atoms is replaced with another atom such as N, P, O, S, As, Ge, Se, Si, Te, etc. Typical heterocycloalkyls include, but are not limited to, imidazolidyl, piperazyl, piperidyl, pyrazolidyl, pyrrolidyl, quinuclidyl, etc. In preferred embodiments, the cycloheteroalkyl is 5-10 membered. Particularly preferred cycloheteroalkyls are morpholino, tetrahydrofuryl, and pyrrolidyl.

"Substituted Heterocycloalkyl": refers to a cycloheteroalkyl radical wherein one or more hydrogen atoms are each independently replaced with another substituent. Typical substituents include, but are not limited to, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl, 6-26 membered alk-heteroaryl, -OR, -SR, -NRR, -CN, -NO₂, -C(O)R, -C(O)OR, -C(O)NRR, -C(NRR)=NR, -C(O)NROR, -C(NRR)=NOR, -NR-C(O)R, -tetrazol-5-yl, -NR-SO₂-R, -NR-C(O)-NRR, -NR-C(O)-OR, -halogen, and -trihalomethyl; where each R is independently -H, (C₁-C₈) alkyl, (C₂-C₈) alkenyl, (C₂-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl, and 6-26 membered alk-heteroaryl as defined herein.

"Aryl": refers to an unsaturated cyclic hydrocarbon radical having a conjugated π electron system. Specifically included within the definition of aryls are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, indane, indene, phenalene, etc. Typical aryl groups include, but are not limited to, penta-2,4-dienyl, phenyl, naphthyl, aceanthrylyl, acenaphthyl, anthracyl, azulenyl, chrysenyl, indacenyl, indanyl, ovalenyl, perylenyl, phenanthrenyl, phenalenyl, picenyl, pyrenyl, pyranthrenyl, rubicenyl, and the like. In preferred embodiments, the aryl group is (C₅-C₂₀) aryl, more preferably (C₅-C₁₀) aryl, and most preferably phenyl.

"Alkaryl": refers to a straight-chain or branched (C₁-C₈) alkyl, (C₂-C₈) alkenyl, or (C₂-C₈) alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with a (C₅-C₂₀) aryl moiety. Typical alkaryl groups include, but are not limited to, benzyl, benzyldiene, benzyldiyne,

benzenobenzyl, naphthalenobenzyl, and the like. In preferred
embodiments, the alkaryl group is (C₆-C₂₆) alkaryl, *i.e.*, the
alkyl, alkenyl, or alkynyl moiety of the alkaryl group is
(C₁-C₆) and the aryl moiety is (C₅-C₂₀). In particularly
5 preferred embodiments the alkaryl group is (C₆-C₁₃), *i.e.*, the
alkyl, alkenyl or alkynyl moiety of the alkaryl group is
(C₁-C₃) and the aryl moiety is (C₅-C₁₀).

"Heteroaryl": refers to an aryl moiety wherein one or
10 more carbon atoms has been replaced with another atom, such as
N, P, O, S, As, Ge, Se, Si, Te, etc. Typical heteroaryl
groups include, but are not limited to acridarsine, acridine,
arsanthridine, arsinole, arsinoline, benzodioxole,
benzothiadiazole, carbazole, β -carboline, chromane, chromene,
15 cinnoline, furan, imidazole, indazole, indole, isoindole,
indolizine, isoarsindole, isoarsinoline, isobenzofuran,
isochromane, isochromene, isoindole, isophosphoindole,
isophosphinoline, isoquinoline, isothiazole, isoxazole,
naphthyridine, perimidine, phenanthridine, phenanthroline,
20 phenazine, phosphoindole, phosphinoline, phthalazine,
piazthiole, pteridine, purine, pyran, pyrazine, pyrazole,
pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine,
quinazoline, quinoline, quinolizine, quinoxaline, selenophene,
tellurophene, thiazopyrrolizine, thiophene, and xanthene. In
25 preferred embodiments, the heteroaryl group is a 5-20 membered
heteroaryl, with 5-10 membered heteroaryl being particularly
preferred.

"Alk-heteroaryl": refers to a straight-chain or branched
30 (C₁-C₈) alkyl, (C₂-C₈) alkenyl, or (C₂-C₈) alkynyl group wherein
one of the hydrogen atoms bonded to a terminal carbon atom is
replaced with a heteroaryl moiety. In preferred embodiments,
the alk-heteroaryl group is a 6-26 membered alk-heteroaryl,

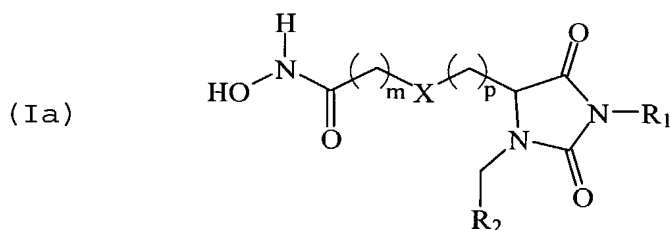
i.e., the alkyl, alkenyl, or alkynyl moiety of the alk-heteroaryl is (C₁-C₆) and the heteroaryl moiety is a 5-20-membered heteroaryl. In particularly preferred embodiments, the alk-heteroaryl is a 6-13 membered alk-heteroaryl, i.e., the alkyl, alkenyl, or alkynyl moiety is (C₁-C₃) and the heteroaryl moiety is a 5-10 membered heteroaryl.

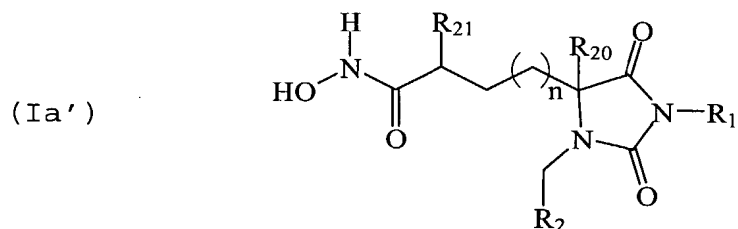
5. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel class of organic compounds capable of inhibiting the enzyme C-proteinase, pharmaceutical compositions comprising one or more of such compounds, and methods of using the compounds to inhibit, regulate, or modulate collagen formation or maturation as a therapeutic approach towards the treatment or prevention of diseases related to, or associated with, unregulated collagen production or maturation.

5.1 The Compounds

In one embodiment, compounds which are capable of inhibiting C-proteinase according to the invention, and which can therefore be used in methods to inhibit, modulate, or regulate collagen production or maturation, or to treat or prevent diseases related to, or associated with, unregulated collagen production or maturation are generally substituted hydantoins according to structural formulae (Ia) and (Ia'):





5 or pharmaceutically acceptable salts thereof, wherein:

m is an integer from 0 to 3 when X is NR_{19} , or an integer from 1 to 3 when X is S or O ;

p is an integer from 1 to 4 when X is NR_{19} , or an integer from 1 to 3 when X is S or O ;

10 n is an integer from 1 to 3;

X is NR_{19} , S or O ;

R_{19} is selected from the group consisting of hydrogen, (C_1-C_5) alkyl, and (C_1-C_5) substituted alkyl;

R_1 and R_2 are each independently selected from the group
 15 consisting of $(\text{C}_1-\text{C}_{10})$ alkyl, $(\text{C}_1-\text{C}_{10})$ substituted alkyl, $(\text{C}_3-\text{C}_{10})$ alkenyl, $(\text{C}_3-\text{C}_{10})$ substituted alkenyl, $(\text{C}_3-\text{C}_{10})$ alkynyl, $(\text{C}_3-\text{C}_{10})$ substituted alkynyl, $(\text{C}_3-\text{C}_{20})$ cycloalkyl, $(\text{C}_3-\text{C}_{20})$ substituted cycloalkyl, 3-20 membered heterocycloalkyl, 3-20 membered substituted heterocycloalkyl, $(\text{C}_5-\text{C}_{20})$ aryl, $(\text{C}_5-\text{C}_{20})$ aryl
 20 independently substituted with one or more Y^1 , alkaryl, alkaryl independently substituted with one or more Y^1 , 5-20 membered heteroaryl, 5-20 membered heteroaryl independently substituted with one or more Y^1 , 6-26 membered alk-heteroaryl, and 6-26 membered alk-heteroaryl independently substituted with one or
 25 more Y^1 ;

R_{20} and R_{21} are each independently selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_{10})$ alkyl, $(\text{C}_6-\text{C}_{26})$ alkaryl, and 6-26 membered alk-heteroaryl; and

each Y^1 is independently selected from the group
 30 consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR,

-C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR,
-NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR,
-NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R,
-SO₃H, -SR, -SO₂-NRR, -OCF₃, and -heteroaryl; where each R is
5 independently selected from the group consisting of hydrogen,
(C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl,
6-20 membered heteroaryl, and 6-26-membered alk-heteroaryl;
with the proviso that the sum of **m** and **p** is 1, 2, 3, or
4.

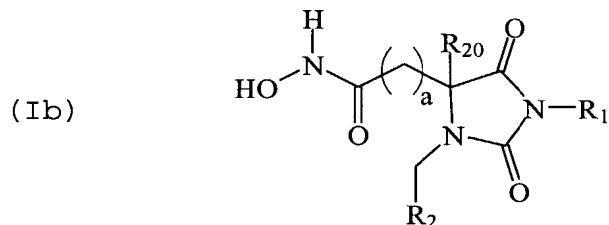
10 In a preferred embodiment, the compounds of the present
invention are compounds according to formula (Ia'), in which
R₂₀ and R₂₁ are each hydrogen and R₁, R₂, and **n** are as defined
for formulae (Ia) and (Ia').

15 In another preferred embodiment, the compounds of the
present invention are compounds according to formula (Ia) in
which **m** and **p** are each 1. In this embodiment, X, R₁, and R₂
are as defined for formulae (Ia) and (Ia').

20 In still another preferred embodiment, the compounds of
the present invention are compounds according to formulae (Ia)
and (Ia'), in which R₁ is adamantyl. In this embodiment, X,
R₂₀, R₂₁, R₂, **m**, **p**, and **n** are as defined for formulae (Ia) and
25 (Ia').

In another preferred embodiment, the compounds of the
present invention are compounds according to formulae (Ia) and
(Ia'), in which R₁ is cyclohexyl. In this embodiment, X, R₂₀,
30 R₂₁, R₂, **m**, **p**, and **n** are as defined for formulae (Ia) and
(Ia').

In a preferred embodiment, the compounds of the invention are generally substituted hydantoin compounds of the structural formula (Ib):

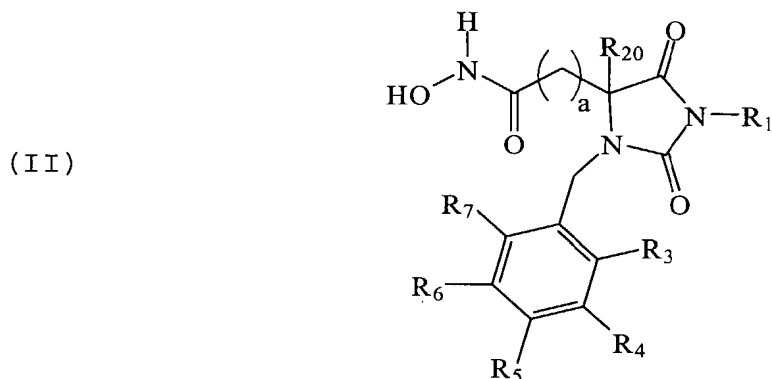


or pharmaceutically acceptable salts thereof, wherein:

a is 2, 3, 4, or 5; and

R_1 , R_2 , and R_{20} are as defined for formula (Ia).

10 One group of preferred compounds according to formula (Ib) are those compounds having structural formula (II):



or pharmaceutically acceptable salts thereof, wherein:

a is as defined for formula (Ib);

R_1 and R_{20} are as defined as in formula (Ia); and

20 R_3 , R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of -hydrogen, -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃, and -tetrazole;

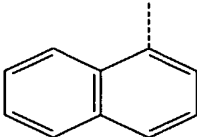
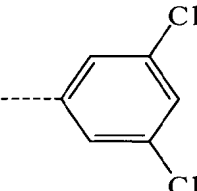
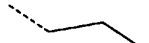
25 where each R is independently selected from the group

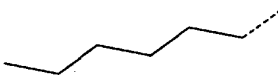
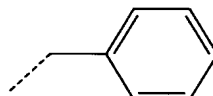
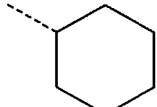
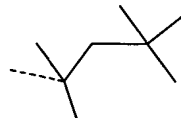
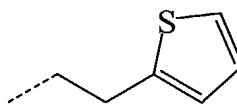
consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl, and 6-26-membered alk-heteroaryl.

One group of preferred compounds according to formula (II) are compounds in which R₂₀ is hydrogen.

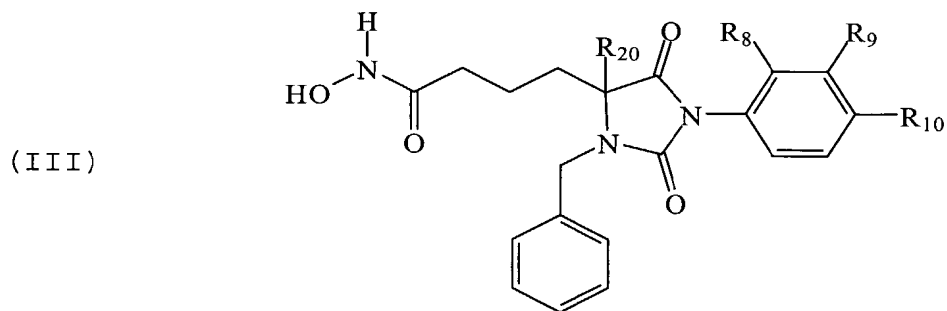
Another group of preferred compounds according to formula (II) are those compounds wherein **a** is 3. Particularly preferred compounds according to this aspect of the invention are those compounds in which R₃, R₄, R₅, R₆, and R₇ are each hydrogen. Particularly preferred compounds according to this aspect of the invention are compounds in which R₂₀ is hydrogen and R₁ is defined in Table 1. In Table 1, the connecting bond is dashed.

Table 1

Compound #	R ₁
101	
102	-adamantyl
103	
104	

Compound #	R ₁
105	
106	
107	
108	
109	

Another group of preferred compounds according to structure (Ib) are those compounds according to structural formula (III):



or pharmaceutically acceptable salts thereof, wherein:

R₈, R₉, and R₁₀ are each independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR,

-CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃, and -tetrazole; where each R is independently selected from the group consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl, and 6-26-membered alk-heteroaryl; and

R₂₀ is as defined for formula (Ia).

Particularly preferred compounds according to structure (III) are compounds in which R₂₀ is -H, and R₈, R₉, and R₁₀ are as defined in Table 2.

Table 2

Compound #	R ₈	R ₉	R ₁₀
110	-H	-H	-H
111	-H	-H	-OCH ₃
112	-OCH ₃	-H	-OCH ₃
113	-H	-H	-NO ₂
114	-phenyl	-H	-H
115	-H	-H	-Cl
116	-H	-CN	-H
117	-H	-Cl	-H
118	-H	-H	-CH ₃
119	-H	-C(O)CH ₃	-H
120	-F	-H	-F
121	-Cl	-H	-Cl
122	-H	-H	-butyl
123	-H	-H	-phenoxy

Compound #	R ₈	R ₉	R ₁₀
124	-H	-H	-butoxy
125	-CH ₃	-CH ₃	-H

Another group of preferred compounds according to structure (Ib) are those compounds wherein R₁ is adamantyl. A particularly preferred class of compounds according to this embodiment are compounds in which

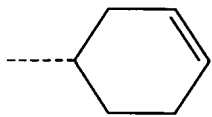
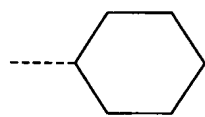
a is 3;

R₂ is selected from the group consisting of (C₁-C₁₀) alkyl, (C₁-C₁₀) substituted alkyl, (C₃-C₁₀) alkenyl, (C₃-C₁₀) substituted alkenyl, (C₃-C₁₀) alkynyl, (C₃-C₁₀) substituted alkynyl, (C₃-C₂₀) cycloalkyl, (C₃-C₂₀) substituted cycloalkyl, (C₅-C₂₀) aryl, (C₅-C₂₀) aryl independently substituted with one or more Y¹, alkaryl, alkaryl independently substituted with one or more Y¹; and Y¹ is as defined in structural formula (Ia); and

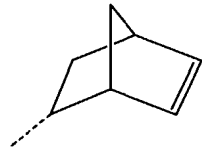
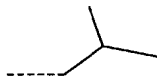
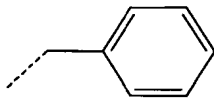


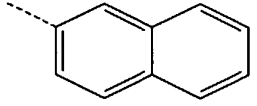
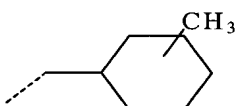
R₂₀ is as defined in formula (Ia).

Particularly preferred compounds in accordance with this class of compounds are compounds in which R₂₀ is hydrogen and R₂ is as defined in Table 3. In Table 3, the connecting bond is dashed.

Table 3

Compound #	R ₂
126	
127	

30

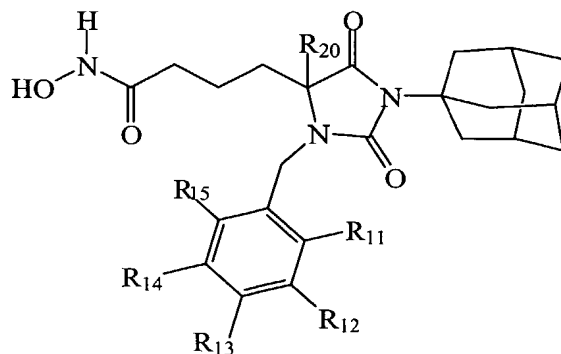
Compound #	R ₂
128	
129	
130	
131	
132	
133	
134	

35

40

Another group of preferred compounds of the present
 45 invention are compounds according to structural formula (IV):

5 (IV)



or pharmaceutically acceptable salts thereof, wherein:

R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃, and -tetrazole; where each R is independently selected from the group consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl, and 6-26-membered alk-heteroaryl; and

R_{20} is as defined in formula (Ia).

Particularly preferred compounds according to formula (IV) are compounds in which R_{20} is -H, and R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are as defined in Table 4:

Table 4

Compound	R_{11}	R_{12}	R_{13}	R_{14}	R_{15}
135	-H	-OCH ₃	-H	-OCH ₃	-H
136	-H	-Cl	-H	-Cl	-H
137	-H	-OH	-H	-H	-OH
138	-OH	-H	-OCH ₃	-H	-H
139	-H	-OCH ₃	-H	-H	-OH
140	-H	-Cl	-H	-H	-OH

Compound	R ₁₁	R ₁₂	R ₁₃	R ₁₄	R ₁₅
141	-H	-OCF ₃	-H	-H	-OH
142	-H	-NO ₂	-H	-H	-OH
143	-OCH ₃	-H	-H	-H	-OH
144	-OCH ₃	-H	-H	-H	-OCH ₃
145	-H	-OH	-H	-OH	-H
146	-H	-Br	-H	-OCH ₃	-OH

A group of preferred compounds according to formula (IV) are those compounds in which R₁₄ and R₁₅ are hydrogen. Particularly preferred compounds according to this class of compounds are compounds in which R₂₀ is hydrogen and R₁₁, R₁₂, and R₁₃ are as defined in Table 5.

Table 5

Compound #	R ₁₁	R ₁₂	R ₁₃
102	-H	-H	-H
148	-H	-H	-Cl
149	-H	-H	-OCH ₃
150	-H	-H	-phenyl
151	-H	-H	-N(CH ₃) ₂
152	-H	-H	-NO ₂
153	-H	-H	-phenoxy
154	-H	-H	-F
155	-OH	-H	-H
156	-H	-H	-CF ₃
157	-H	-H	-OH
158	-H	-H	-CH ₃
159	-H	-OCH ₃	-OCH ₃
160	-F	-H	-F

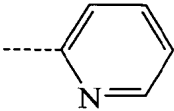
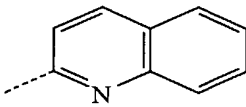
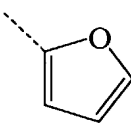
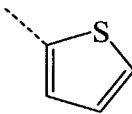
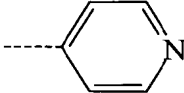
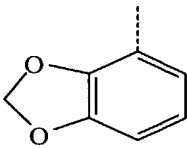
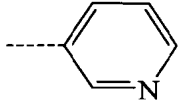
Compound #	R ₁₁	R ₁₂	R ₁₃
161	-H	-OH	-H
162	-OCH ₃	-OCH ₃	-H
163	-OCH ₃	-H	-H
164	-OH	-H	-OH
165	-NO ₂	-H	-H
166	-H	-OH	-OCH ₃
167	-OH	-OH	-H
168	-OH	-OCH ₃	-H
169	-COOH	-H	-H
170	-H	-CH ₃	-H
171	-H	-OCH ₃	-H
172	-H	-Cl	-H
173	-H	-COOH	-H

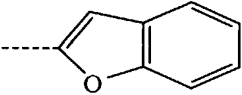
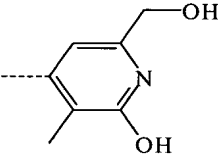
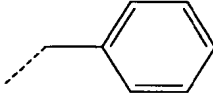
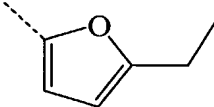
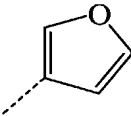
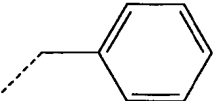
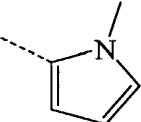
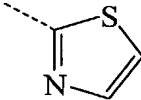
A group of preferred compounds according to formula (Ib) are those compounds in which R₂ is selected from the group consisting of 5-20 membered heteroaryl, 5-20 membered heteroaryl independently substituted with one or more Y¹, 3-20 membered heterocycloalkyl, 3-20 membered substituted heterocycloalkyl, 6-26 membered alk-heteroaryl, and 6-26 membered alk-heteroaryl independently substituted with one or more Y¹; and

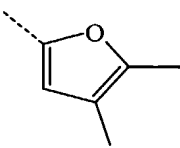
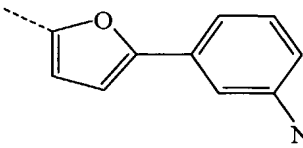
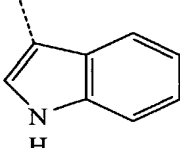
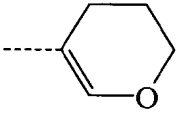
Y¹ is as defined in formula (Ia).

Particularly preferred compounds according to this embodiment are compounds in which a is 3. Preferred compounds in this class include compounds of Table 6. In Table 6, the connecting bond is dashed.

Table 6

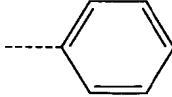
Compound #	R ₂
174	
175	
176	
177	
178	
179	
180	

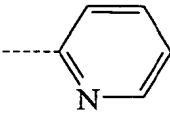
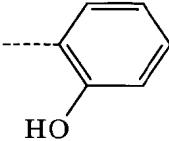
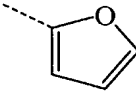
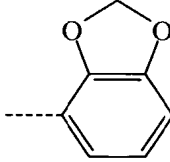
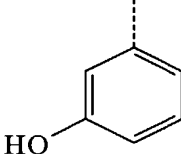
Compound #	R ₂
181	
182	
183	
184	
185	
186	
187	
188	

Compound #	R ₂
189	
190	
191	
192	

Another group of preferred compounds according to structural formula (Ib) are those compounds wherein R₁ is cyclohexyl. Particularly preferred compounds according to this aspect of the invention are those compounds in which **a** is 3. Even more preferred are compounds in this embodiment in which R₂₀ is hydrogen and R₂ is as defined in Table 7. In Table 7, the connecting bond is dashed.

Table 7

Compound #	R ₂
107	

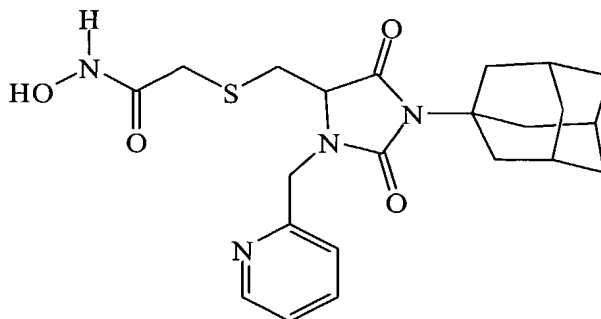
Compound #	R ₂
194	
195	
196	
197	
198	

Yet another group of preferred compounds according to formula (Ia) are those compounds in which X is S.

Particularly preferred compounds in which X is S are those

compounds in which **m** is 1, **p** is 1, and R₁ is adamantyl. Of the compounds of this class, compound 199 is particularly preferred:

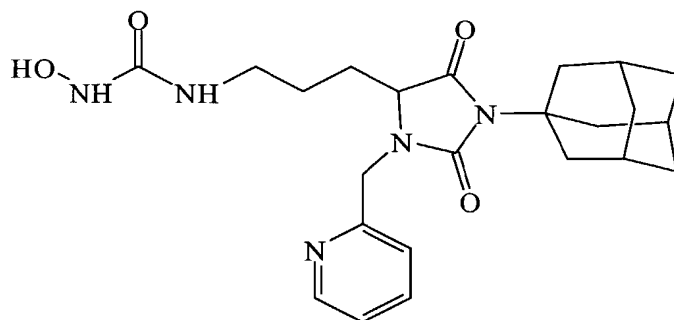
199



5

Another group of preferred compounds according to formula (Ia) are those compounds in which X is NR_1 . Particularly preferred compounds in this embodiment are those compounds in which **m** is 0, **p** is 3, and R_1 is adamantyl. A particularly preferred compound in this embodiment is compound 200:

200



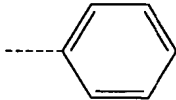
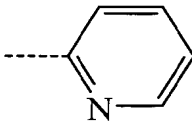
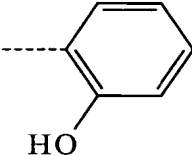
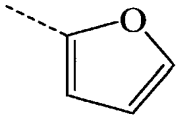
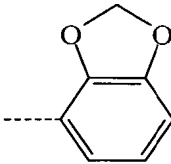
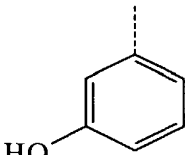
15

Another group of preferred compounds according to formula (Ia) are those compounds in which X is O.

A group of preferred compounds according to formula (Ia') are those compounds in which R_1 is cyclohexyl, R_{20} and R_{21} are each methyl, and R_2 is as defined in Table 8. In Table 8, the connecting bond is dashed.

25

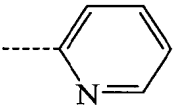
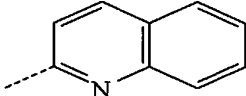
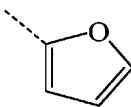
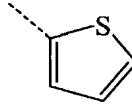
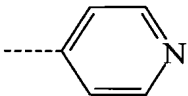
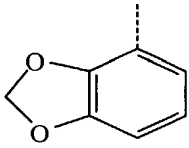
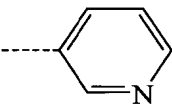
Table 8

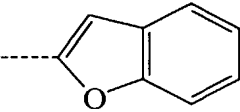
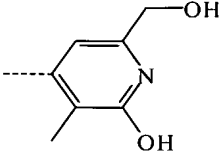
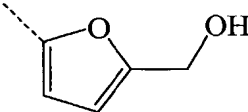
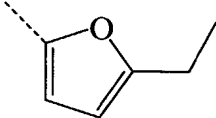
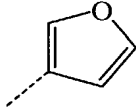
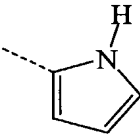
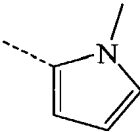
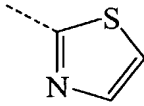
Compound #	R ₂
H1	
H2	
H3	
H4	
H5	
H6	

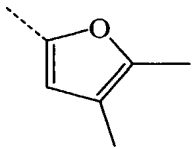
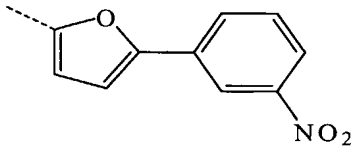
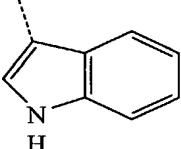
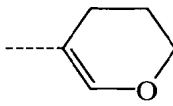
Another group of preferred compounds according to formula (Ia') are those compounds in which R₁ is adamantyl, R₂₀ and R₂₁

are each methyl, and R_2 is as defined in Table 9. In Table 9, the connecting bond is dashed.

Table 9

Compound #	R_2
H7	
H8	
H9	
H10	
H11	
H12	
H13	

Compound #	R ₂
H14	
H15	
H16	
H17	
H18	
H19	
H20	
H21	

Compound #	R ₂
H22	
H23	
H24	
H25	

The chemical structural formulae referred to herein may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism, and/or stereo isomerism. As the formulae drawings within this specification can only represent one of the possible tautomeric, conformational isomeric, geometric isomeric, or stereo isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, geometric isomeric, or stereo isomeric forms which exhibit biological or pharmacological activity as defined herein.

The compounds of the invention may be in the form of free acids, free bases, or pharmaceutically effective acid addition or base addition salts. Such acid addition salts can be readily prepared by treating a compound with a pharmaceutically acceptable acid. Pharmaceutically acceptable

acids include, by way of example and not limitation, inorganic acids such as hydrohalic acids (hydrochloric, hydrobromic, etc.), sulfuric acid, nitric acid, phosphoric acid, etc.; and organic acids such as acetic acid, propanoic acid,

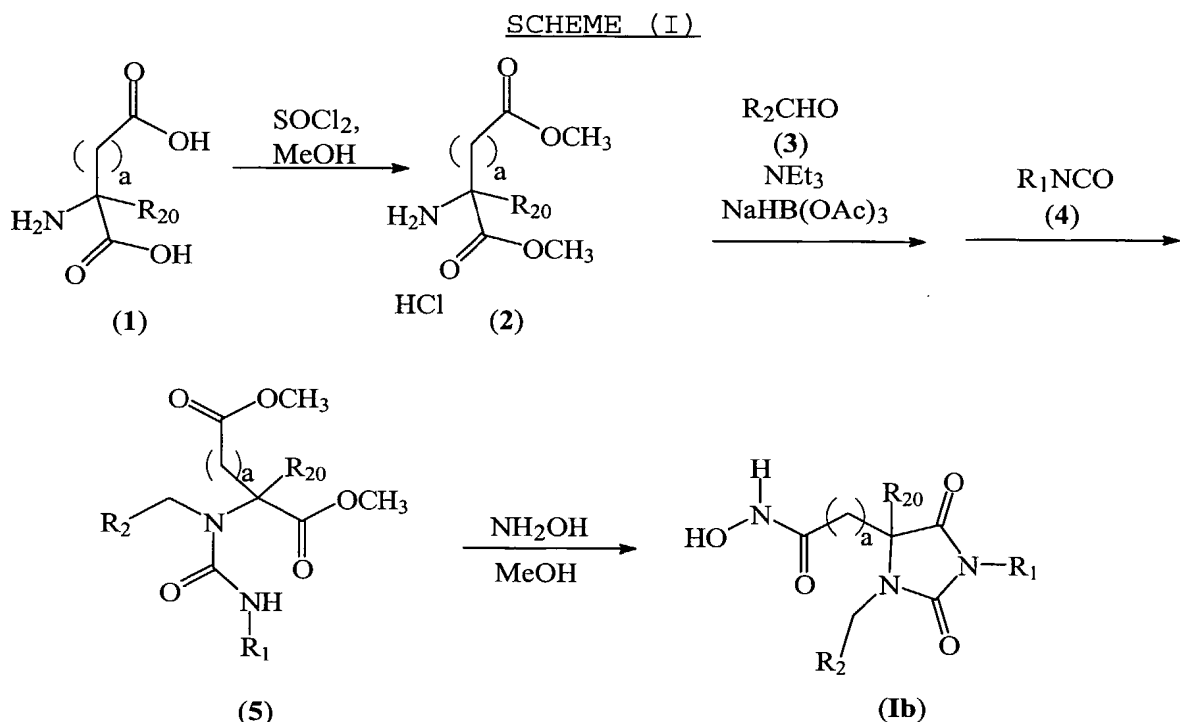
5 2-hydroxyacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, propandioic acid, butandioic acid, etc. Conversely, the acid addition salt can be converted into the free base form by treatment with alkali. Appropriate base addition salts can be readily prepared by treating a compound with a
10 pharmaceutically acceptable base.

In addition to the above compounds and their pharmaceutically acceptable salts, the invention is further directed, where applicable, to solvated as well as to unsolvated forms of the compounds (e.g. hydrated forms)
15 exhibiting biological or pharmacological activity as defined herein.

5.2 METHODS OF MAKING THE COMPOUNDS

The compounds of the invention may be prepared by any
20 process known to be applicable to the preparation of chemical compounds. Suitable processes are well-known in the art. Preferred processes are illustrated by the representative examples. Necessary starting materials may be obtained commercially or by standard procedures of organic chemistry.

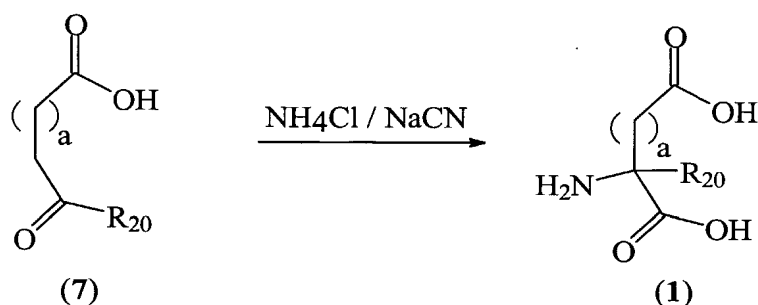
25 By way of example, the compounds of the invention can be conveniently prepared by schemes (I) thru (XII) below:



In Scheme (I), compounds of formula (Ib) are synthesized and a , R_1 , R_2 , and R_{20} are as defined for formula (Ib).

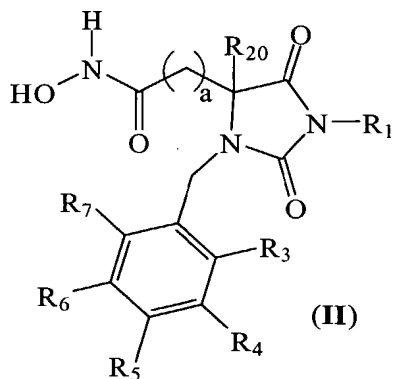
According to scheme (I), D,L-2-amino-(C_2 - C_5) alkanedioic acid **1** was mixed with SOCl_2 in MeOH to yield D,L-2-amino-(C_2 - C_5) alkanedioic acid dimethyl ester hydrochloride **2**. To compound **2** (0.5 mM) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mM), aldehyde **3** (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then isocyanate **4** (0.55 mM) was added. The mixture was shaken for an additional twelve hours and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **5**. Residue **5** was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield compound of formula (Ib). Compound of formula (Ib) was triturated in ether/hexane (1:1, 5 mL), and dried *in vacuo*.

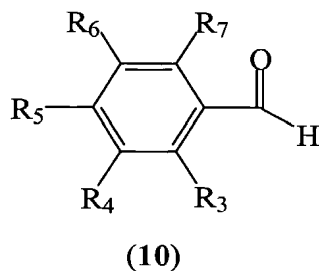
D,L-2-amino-(C₂-C₅)alkanedioic acid compounds **1** in which R₂₀ is hydrogen are commercially available. Compounds **1** in which R₂₀ is a (C₁-C₁₀) alkyl, (C₆-C₂₆) alkaryl, and 6-26 membered alk-heteroaryl are synthesized by Strecker synthesis as follows:



See, for example, Gal *et al.*, 1954, J. Am. Chem. Soc. 76, 4181, Izumi *et al.*, 1965, Bull. Chem. Soc. Jpn., 38, 1338, Weinges *et al.*, 1971, Chem. Ber., 104, 3594.

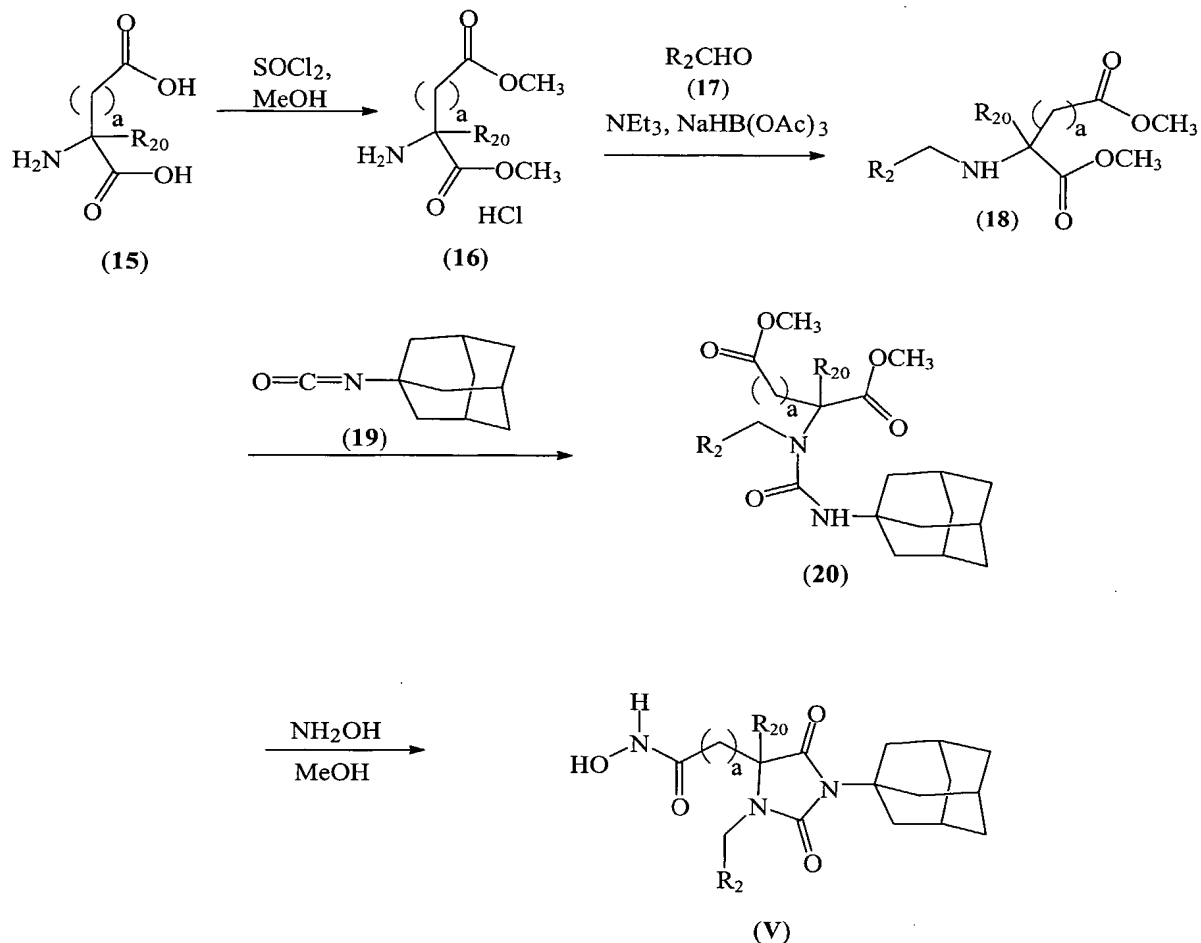
SCHEME (II)





In Scheme (II), compounds of formula (II) are synthesized. Accordingly, R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_{20} and **a** are
5 as defined in formula (II). Compounds of Scheme (II) are synthesized according to Scheme (I) by using compound **10** for aldehyde **3**.

SCHEME (III)

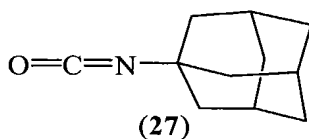
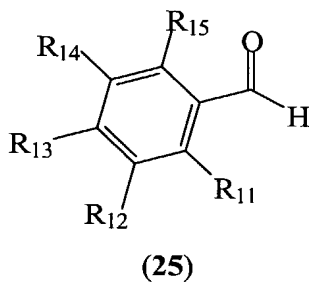


In Scheme (III), **a**, and R₂₀ are as defined for formula (Ib). R₂ is selected from the group consisting of (C₁-C₁₀) alkyl, (C₁-C₁₀) substituted alkyl, (C₃-C₁₀) alkenyl, (C₃-C₁₀) substituted alkenyl, (C₃-C₁₀) alkynyl, (C₃-C₁₀) substituted alkynyl, (C₃-C₂₀) cycloalkyl, (C₃-C₂₀) substituted cycloalkyl, (C₅-C₂₀) aryl, (C₅-C₂₀) aryl independently substituted with one or more Y¹, alkaryl, and alkaryl independently substituted with one or more Y¹; where Y¹ is as defined in structural formula (Ia). According to Scheme (III), D,L-2-amino-(C₂-C₅) alkanedioic acid **15** was mixed with SOCl₂ in MeOH to yield D,L-2-amino-(C₂-C₅) alkanedioic acid dimethyl ester hydrochloride **16**. To compound **16** (0.5 mM) in CH₂Cl₂ (5 mL) was added triethylamine (0.55 mM), aldehyde **17** (0.55 mM), and sodium

triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then adamantyl-isocyanate **19** (0.55 mM) was added. The mixture was shaken for an additional twelve hours, and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, concentrated, and dried to yield residue **20**. Residue **20** was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield compound of formula (V). Compound of formula (V) was triturated in ether/hexane (1:1, 5 mL), and dried *in vacuo*.

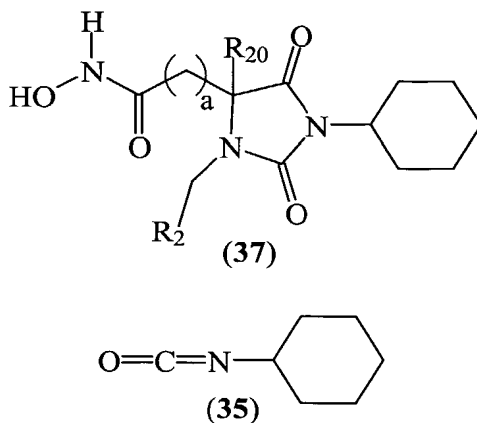
D,L-2-amino-($\text{C}_2\text{-C}_5$) alkanedioic acid compounds **15** in which R_{20} is hydrogen are commercially available. Compounds **15** in which R_{20} is other than hydrogen may be prepared by Strecker synthesis as described in Scheme (I).

SCHEME (IV)



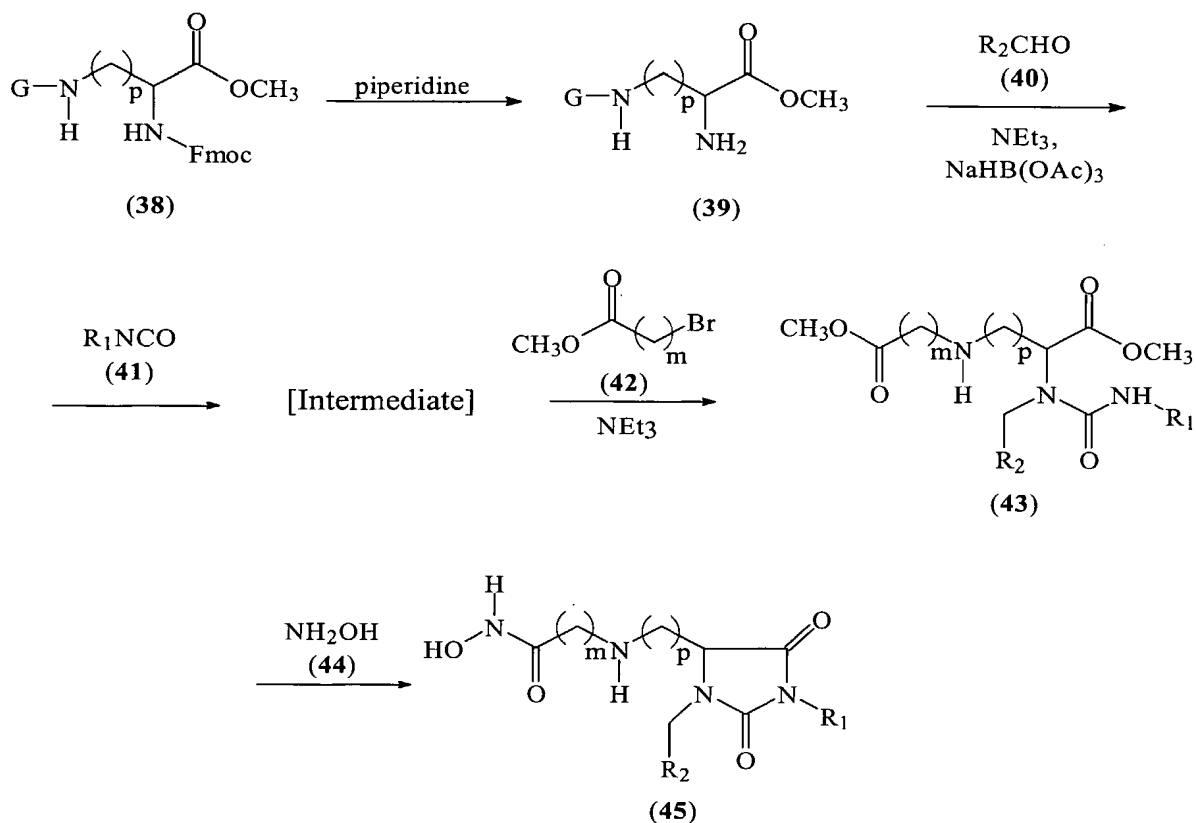
In Scheme (IV), compounds of formula (IV) are synthesized. Accordingly, **a**, R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , and R_{20} are as defined in formula (IV). Compounds are synthesized as described in Scheme (I) by using aldehyde **25** for compound **3** and Adamantyl-isocyanate **27** for compound **4**.

SCHEME (V)



In Scheme (V), **a**, R_{20} , and R_2 are as defined in formula (Ib). In Scheme (V), compounds **37** are synthesized using the synthesis described in Scheme (I), where cyclohexyl-isocyanate **35** is used for compound **4**.

SCHEME (VI)



In Scheme (VI), R_1 , R_2 , m , and p are as defined in formula (Ia) and Fmoc is 9-fluorenylmethyl carbamate. Suitable amino protecting groups, G , may be found, for example, in Greene & Wuts, 1991, Protective Groups in Organic Synthesis, John Wiley & Sons, New York. In a preferred embodiment, G is tert-butoxycarbonyl.

According to Scheme (VI), compounds of formula (Ia) in which X is NH are synthesized. Compound 38 was mixed with piperidine to yield compound 39. To compound 39 (0.5 mM) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mM), aldehyde 40 (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then isocyanate 41 (0.55 mM) was added. The mixture was

shaken for an additional twelve hours and then quenched with 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield intermediate.

Intermediate, in which the protecting group G was tert-

5 butoxycarbonyl, was treated with trifluoroacetic acid in CH_2Cl_2 (5 percent, 5 mL) for five hours and then concentrated. The resulting residue was dissolved in 5 mL of CH_2Cl_2 and

triethylamine and compound **42** were added. The mixture was stirred for twelve hours at room temperature. The reaction

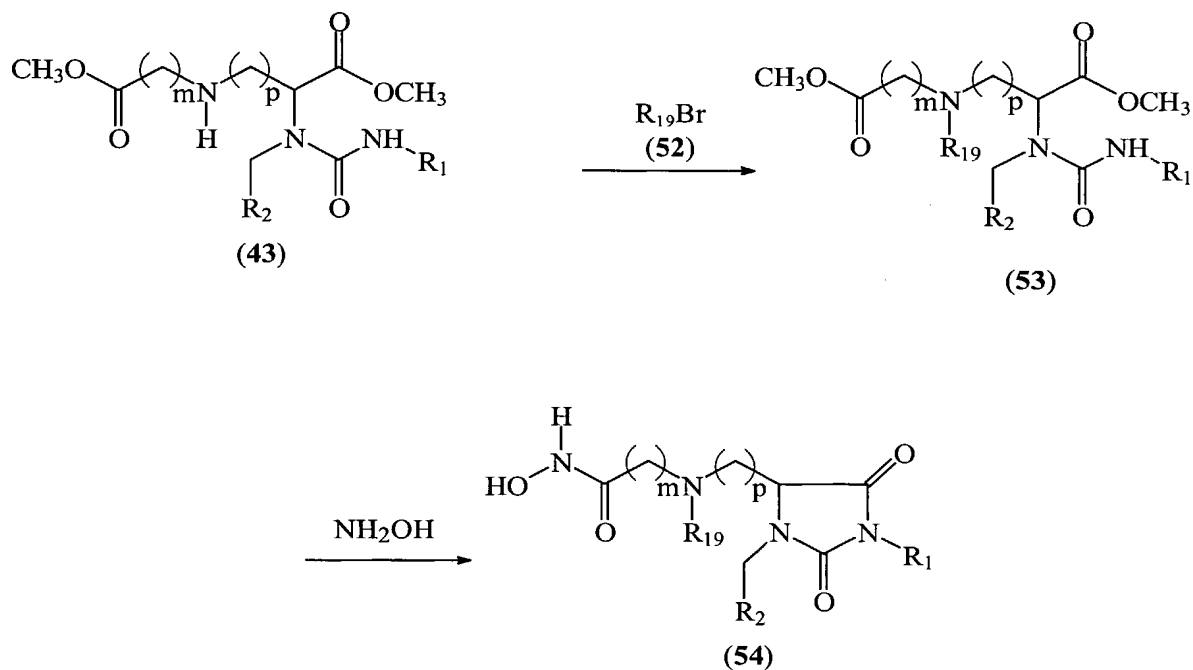
10 mixture was concentrated and purified by silica gel

chromatography to give residue **43**. Residue **43** was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM)

44 for twelve hours, and then quenched with 2 mL of 1N HCl,

and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5

15 mL), dried over MgSO_4 , filtered, and concentrated to yield compound **45**.

SCHEME (VII)

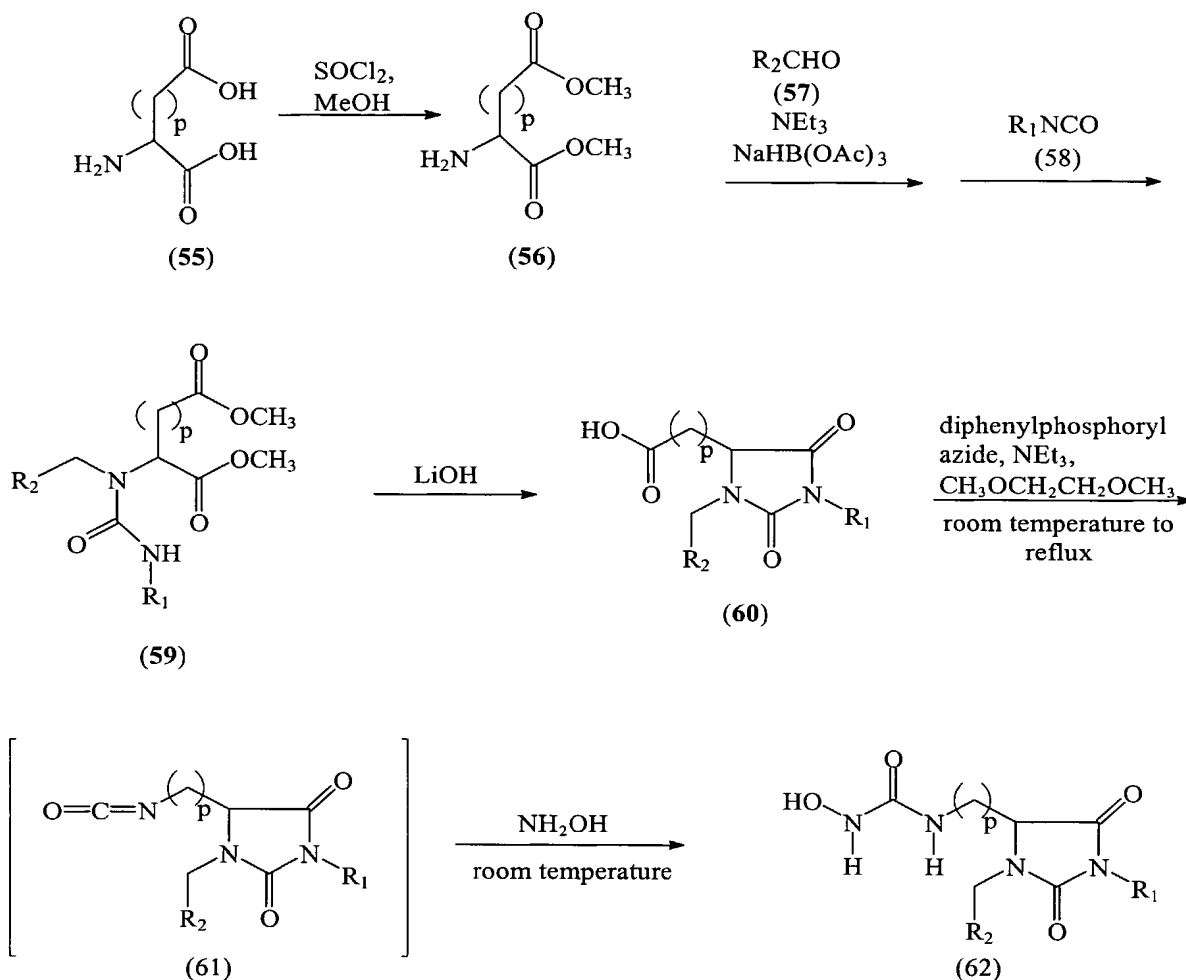
5

In Scheme (VII), compounds of formula (Ia) in which X is NR_{19} are synthesized. Accordingly, m , p , R_1 , R_2 , and R_{19} are as defined in formula (Ia). According to Scheme (VII), compound 43, which was synthesized as detailed in Scheme (VI), was

10 mixed with compound 52 to yield compound 53. Compound 53 was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to

15 yield 54.

SCHEME (VIII)



In Scheme (VIII), compounds of formula (Ia) in which X is
 5 NH are synthesized. Accordingly, *p*, R₁, and R₂ are as defined
 in formula (Ia). According to Scheme (VIII), D,L-2-amino-(C₂-
 C₅) alkanedioic acid **55** is mixed with SOCl₂ in MeOH to yield
 D,L-2-amino-(C₂-C₅) alkanedioic acid dimethyl ester
 hydrochloride **56**. To compound **56** (0.5 mM) in CH₂Cl₂ (5 mL) was
 10 added triethylamine (0.55 mM), aldehyde **57** (0.55 mM), and
 sodium triacetoxyborohydride (0.7 mM). The reaction mixture
 was shaken at room temperature for six hours, and then
 isocyanate **58** (0.55 mM) was added. The mixture was shaken for
 an additional twelve hours and then quenched with 1 mL of 1 N

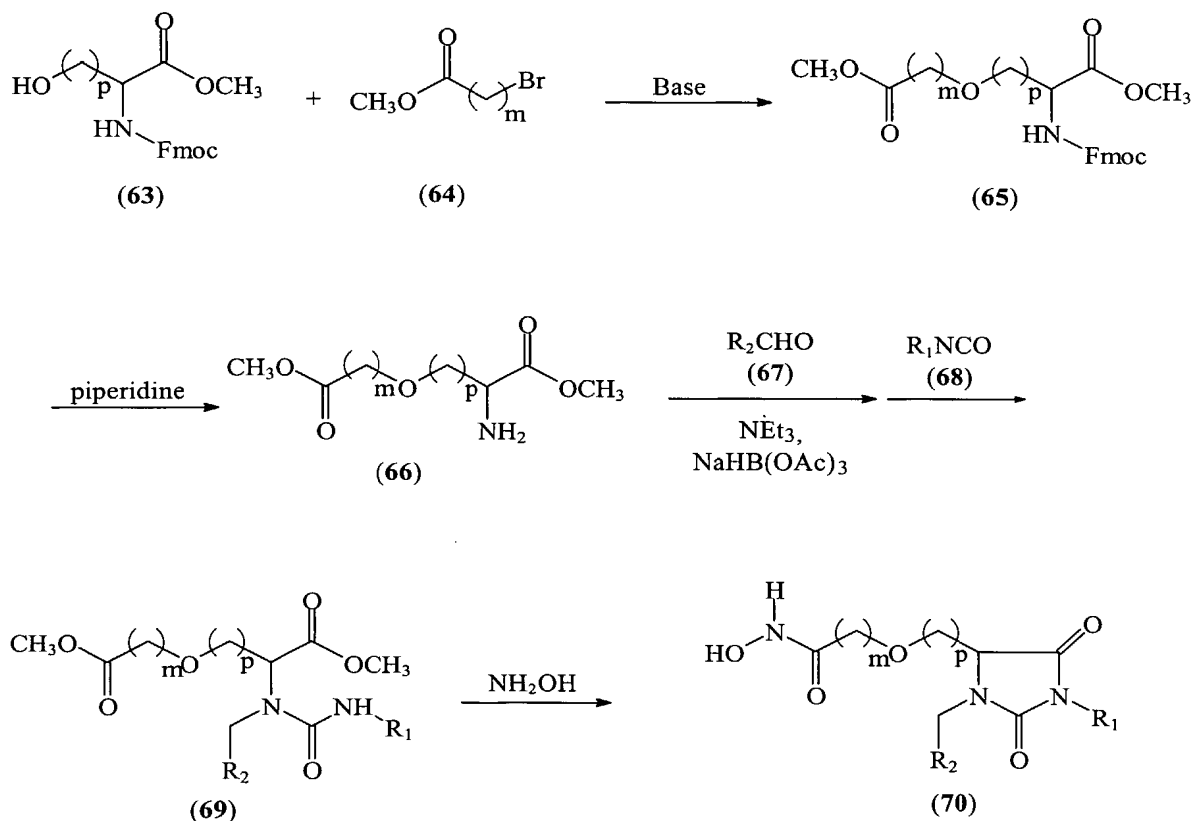
HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, concentrated, and dried to yield residue 59. Residue 59 was treated with LiOH to yield compound 60.

Compound 60 was mixed with diphenylphosphoryl azide,

5 triethylamine, and ethylene glycol and refluxed at room temperature to form isocyanate 61. Isocyanate 61 was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL),

10 dried over MgSO_4 , filtered, and concentrated to yield N-hydroxy-urea 62.

SCHEME (IX)



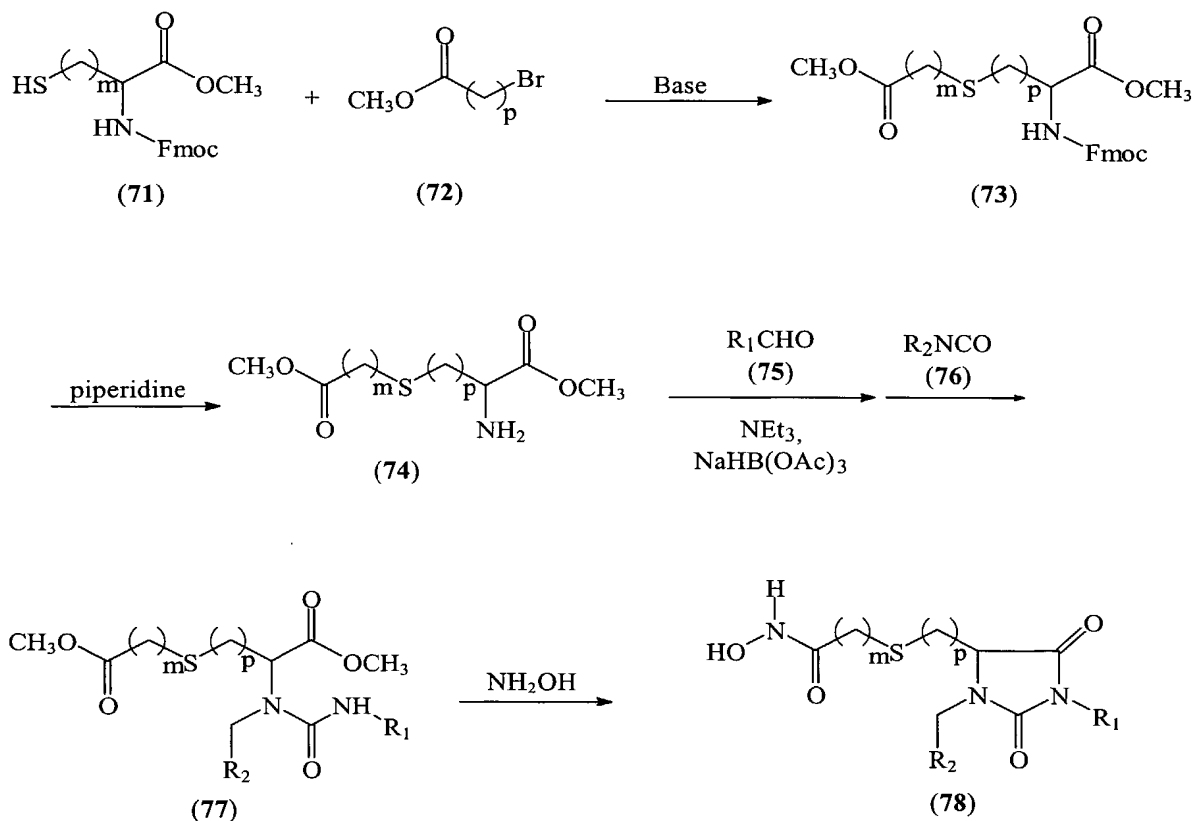
In Scheme (IX), compounds of formula (Ia) in which X is O are synthesized. Accordingly, R_1 , R_2 , m , and p are as defined for formula (Ia) and Fmoc is 9-fluorenylmethyl carbamate.

According to Scheme (IX), Compound 63 was combined with compound 64 in the presence of a base to yield compound 65. One suitable base was sodium hydride. Compound 65 was deprotected using piperidine to yield the corresponding free amine 66. Additionally, deprotection of the Fmoc group of compound 65 may be effected by the use of other amine bases as described in Greene and Wuts, *supra*, pages 318-319. To compound 66 (0.5 mM) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mM), aldehyde 67 (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then isocyanate

68 (0.55 mM) is added. The mixture was shaken for an additional twelve hours and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **69**.

5 Residue **69** was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 ml of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **70**. Residue **70** was triturated
 10 in ether/hexane (1:1, 5 mL), and dried *in vacuo*.

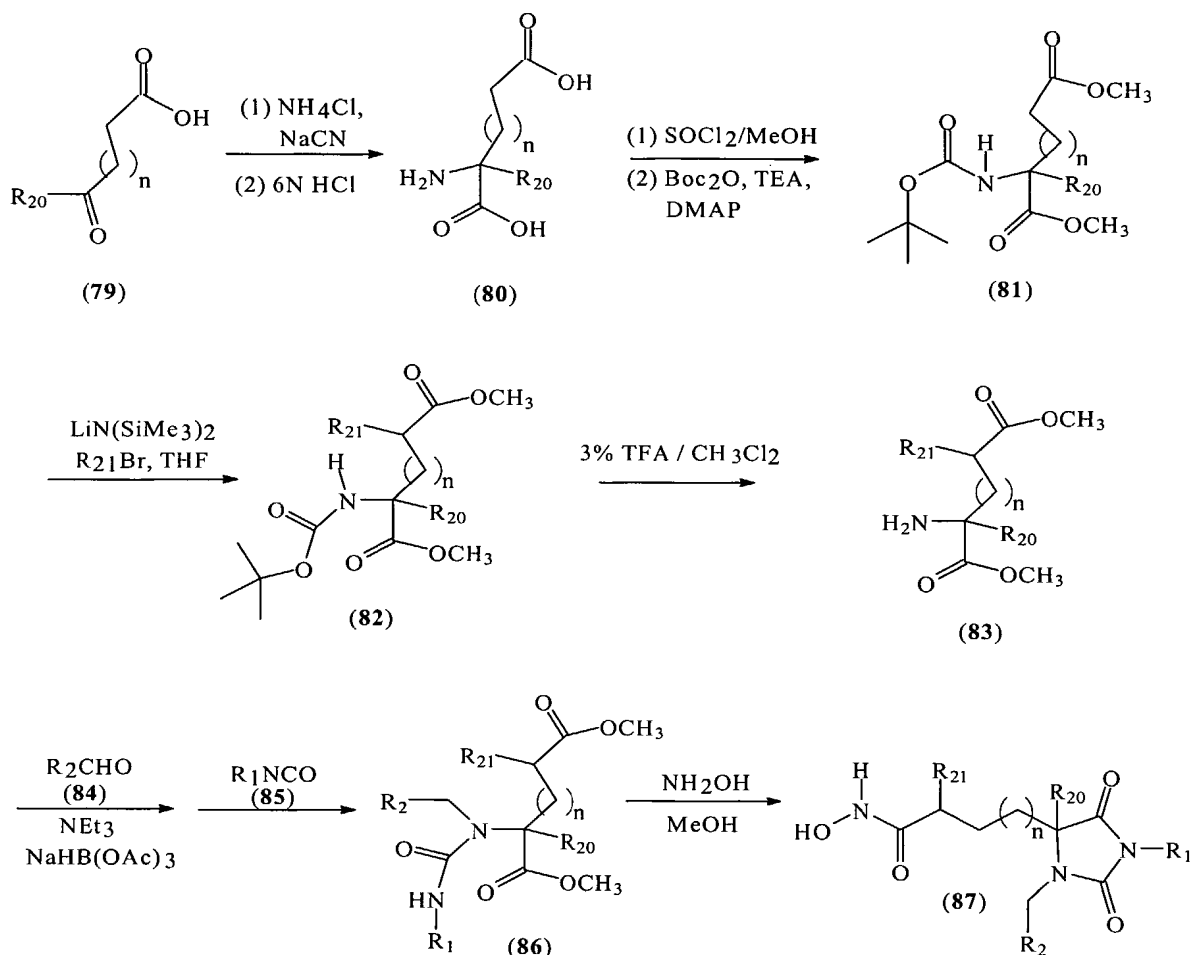
SCHEME (X)



15 In Scheme (X), compounds of formula (Ia) in which X is S are synthesized. Accordingly, R_1 , R_2 , m, and p are as defined for formula (Ia) and Fmoc is 9-fluorenylmethyl carbamate.

According to Scheme (X), compound **71** was combined with compound **72** in the presence of a base to yield compound **73**. One suitable base was sodium hydride. Compound **73** was deprotected using piperidine to yield the corresponding free amine **74**. Additionally, deprotection of the Fmoc group of compound **74** may be effected by the use of other amine bases as described in Greene and Wuts, *supra*, pages 318-319. To compound **74** (0.5 mM) in CH₂Cl₂ (5 mL) was added triethylamine (0.55 mM), aldehyde **75** (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then isocyanate **76** (0.55 mM) was added. The mixture was shaken for an additional twelve hours and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO₄, filtered, concentrated and dried to yield residue **77**. Residue **77** was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH₂Cl₂. The organic phase was washed with water (5 mL), dried over MgSO₄, filtered, and concentrated to yield residue **78**. Residue **78** was triturated in ether/hexane (1:1, 5 mL), and dried in *vacuo*.

SCHEME (XI)



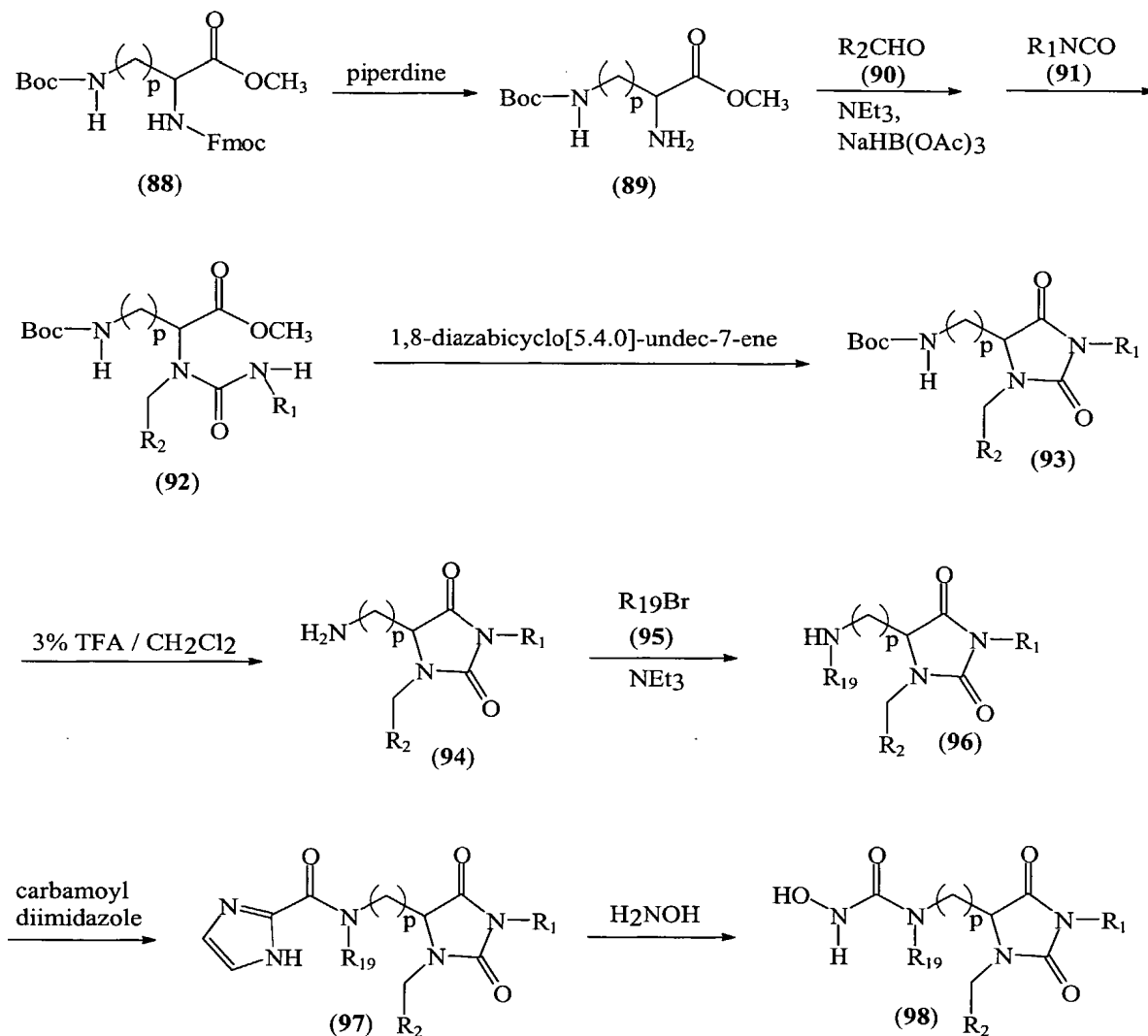
In Scheme (XI), compounds of formula (Ia') are synthesized.

- 5 Accordingly, R_1 , R_2 , R_{20} , R_{21} , and n are as defined in formula (Ia'). According to scheme (XI), D,L-2-amino-(C_2 - C_5)alkanedioic acid **80** is prepared by Strecker synthesis from compound **79**. See, for example, Gal et al., 1954, J. Am. Chem. Soc. 76, 4181, Izumi et al., 1965, Bull. Chem. Soc. Jpn., 38,
 10 1338, Weinges et al., 1971, Chem. Ber., 104, 3594. Compound **80** is mixed with SOCl_2 in MeOH to yield D,L-2-amino-(C_2 - C_5)alkanedioic acid dimethyl ester hydrochloride, the amino group of which was protected by tert-butylcarbamate (Boc) by reacting with Boc_2O in the presence of
 15 triethylamine (TEA) and demethylaminopyridine (DMAP) to yield

81. Compound **81** was enolated by treating with lithium hexamethyldisilylamide $[\text{LiN}(\text{SiMe}_3)_2]$, followed by the addition of R_{21}Br to give compound **82**. The Boc (tert-butylcarbonate) protecting group of compound **82** was removed by treating with
5 three percent trifluoroacetic acid (TFA) in methylene chloride to furnish compound **83**. To compound **83** (0.5 mM) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mM), aldehyde **84** (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then
10 isocynate **85** (0.55 mM) was added. The mixture was shaken for an additional twelve hours and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **86**. Residue **86** was treated with freshly prepared hydroxylamine
15 solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **87**. Residue **87** was triturated in ether/hexane (1:1, 5 mL), and dried *in vacuo*.

20

SCHEME (XII)



In Scheme (XII), compounds of formula (Ia) in which X is NR₁₉, and **m** is 0 are synthesized. Accordingly, R₁, R₂, and **p** are as defined in formula (I).

According to Scheme (XII), compound **88** is mixed with piperidine to yield compound **89**. To compound **89** (0.5 mM) in CH₂Cl₂ (5 mL) is added triethylamine (0.55 mM), aldehyde **90** (0.55 mM), and sodium triacetoxyborohydride (0.7 mM). The reaction mixture is shaken at room temperature for 6 hours,

and then isocyanate **91** (0.55 mM) is added. The mixture is shaken for additional 12 hours and the quenched with 1 N HCl. The organic phase is washed and dried to yield **92**. The cyclization of compound **92** is carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to afford **93**. Tert-butoxycarbonyl (Boc) protecting group is removed upon treatment with 3% trifluoroacetic acid (TFA)/ CH₂Cl₂ to provide compound **94**, which, after being concentrated several times in ether, in turn reacts with **95** to yield compound **96**. Compound **96** is then reacted with carbonyl diimidazole to give compound **97**. Compound **97** is treated with freshly prepared hydroxylamine solution to yield compound **98**.

5.3 BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY

An individual compound's relevant activity and potency as an inhibitor of C-proteinase, to regulate or modulate collagen production or maturation and/or to treat disorders associated with unregulated collagen production, may be determined using available techniques.

Typically, active compounds of the invention will inhibit 50% of the activity of C-proteinase at concentrations in the range of 100 micromolar (μ M) or less (i.e., those compounds exhibiting an IC₅₀ of 100 μ M or less) using standard biochemical assays, e.g., Dickson, 1953, Biochem. J. 55:170-171; Knight et al., 1992, FEBS 296:263-266. Those of skill in the art will appreciate that compounds exhibiting lower inhibitory concentrations (IC₅₀s) are generally preferred for pharmacological applications; thus, preferably active compounds will exhibit IC₅₀s that are preferably less than 10 μ M, more preferably less than 1 μ M, even more preferably less than 100 nanomolar (nM), and most preferably less than about 10 nM or 1 nM. However, as compounds which exhibit IC₅₀s in the millimolar (mM) range can provide consequential

pharmacological benefits, compounds which exhibit IC_{50} s as high as 1 mM to 10 mM are considered to possess biological or pharmacological activity.

Alternatively, an *in vitro* procollagen assay may be used to determine the level of activity and effect of different compounds of the present invention on C-proteinase activity. In the procollagen assay, about 125 μ g radiolabeled (14 C) procollagen is added to 10 units/ml of chicken C-proteinase in a solution of 0.1 M Tris-HCl, 0.1 M NaCl, 0.02% Brij-35, and 5 mM $CaCl_2$ in a total volume of 10 μ l. The reaction is allowed to proceed for 15 minutes at 35°C and is stopped with one-half volume of 3x stop/loading buffer (30 mM EDTA, 30% glycerol, 6% SDS, 0.006% Bromophenol-blue). Subsequently, the samples are heated to 100°C for 4 minutes, and resolved by SDS-PAGE (Novex) using 6% polyacrylamide gels. The protein bands are detected by autoradiography. The amount of enzyme activity is based on the disappearance of the band corresponding to uncleaved procollagen. The IC_{50} of inhibitors can be determined by plotting the percent activity versus inhibitor concentration and estimating the inhibitor concentration which results in 50% activity.

5.4 Indications

Disorders associated with unregulated collagen production or maturation can be treated with the compounds and compositions of the present invention. While not intending to be bound by any particular theory, it is believed that when administered to an animal subject, including a human, the compounds of the invention inhibit C-proteinase *in vivo*, thereby effectively modulating, regulating, or inhibiting collagen production or maturation. As a consequence, the compounds are able to treat or prevent disorders associated with unregulated collagen production or maturation.

Collagen-related disorders which can be treated or prevented according to the invention include pathological fibrosis or scarring, such as endocardial sclerosis, idiopathic interstitial fibrosis, interstitial pulmonary fibrosis, perimuscular fibrosis, Symmers' fibrosis, pericentral fibrosis, hepatitis, dermatofibroma, biliary cirrhosis, alcoholic cirrhosis, acute pulmonary fibrosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney fibrosis/glomerulonephritis, kidney fibrosis/diabetic nephropathy, scleroderma/systemic, scleroderma/local, keloids, hypertrophic scars, severe joint adhesions/arthritis, myelofibrosis, corneal scarring, cystic fibrosis, muscular dystrophy (Duchenne's), cardiac fibrosis, muscular fibrosis/retinal separation, esophageal stricture, and Peyronie's disease, etc. Further, fibrotic disorders may be induced or initiated by surgery such as scar revision/plastic surgeries, glaucoma, cataract fibrosis, corneal scarring, joint adhesions, graft vs. host disease, tendon surgery, nerve entrapment, Dupuytren's contracture, OB/GYN adhesions/fibrosis, pelvic adhesions, peridural fibrosis, and restenosis. Still further fibrotic disorders may be induced by chemotherapy, including, for example, lung fibrosis and the like.

5.5 Pharmaceutical Formulations And Routes Of Administration

The compounds described herein, or pharmaceutically acceptable addition salts or hydrates thereof, can be delivered to a subject, including a human, using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, and intestinal

administration, and parenteral administration, including intramuscular, subcutaneous, and intravenous injections.

The compounds described herein, or pharmaceutically acceptable salts and/or hydrates thereof, may be administered singly, in combination with other compounds of the invention, and/or in cocktails combined with other therapeutic agents. Of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

For example, the compounds of the invention can be administered in cocktails containing agents used to treat pain and other symptoms and side effects commonly associated with fibrotic disorders. The compounds can also be administered in cocktails containing other agents commonly used to treat fibrotic disorders.

The active compound(s) may be administered *per se* or in the form of a pharmaceutical composition containing the active compound(s) and one or more pharmaceutically acceptable carriers, excipients, or diluents. Administered compounds may be enantiomerically pure, or may be mixtures of enantiomers. Pharmaceutical compositions for use in accordance with the present invention may be formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be

permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft,

sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in a mixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection
5 suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl
10 cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder
15 form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter
20 or other glycerides.

In addition to the formulations previously described, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or
25 intramuscularly), intramuscular injection, or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a
30 sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited

to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

5 **5.5.1 Effective Dosage.**

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically
10 effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided
15 herein.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range
20 that includes the IC_{50} as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the C-proteinase activity). Such information can be used to more accurately determine useful doses in humans.

25 A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or
30 experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic

index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. See, e.g., Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the C-proteinase inhibiting effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; for example, the concentration necessary to achieve 50-90% inhibition of the C-proteinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90%, and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's

weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

5.5.2 Packaging

5 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as in a blister pack. The pack or dispenser device may be accompanied
10 by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the
15 label may include treatment of arthritis or any other fibrotic disorder.

20 6. EXAMPLE: COMPOUND SYNTHESSES

 The compounds of the present invention may be synthesized according to known techniques. The following represent preferred methods for synthesizing certain compounds of the invention.

25

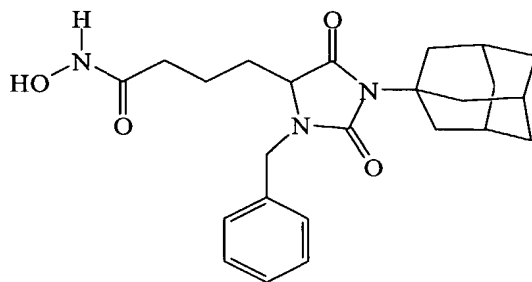
Preparation of Compounds 6.1 through 6.17 (hydroxamation reaction): To a solution of D,L-2-aminoadipic acid dimethyl ester hydrochloride (0.5 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mmol), aldehyde (0.55 mmol), and sodium
30 triacetoxyborohydride (0.7 mmol). The reaction mixture was shaken at room temperature for 6 hours, the corresponding isocyanate (0.55 mM) was added, and the mixture was shaken for an additional 12 hours, and then quenched with 1 mL of 1 N

HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, concentrated, and dried. The residue was treated with a freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for 12 hours, and then quenched with 2 mL of 1 N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated. The residue was triturated in ether/hexane (1:1, 5 mL), and dried *in vacuo* to leave the compound as a colorless foam.

Preparation of hydroxylamine solution: A solution of potassium hydroxide (840 mg, 15 mM) in 5 mL of methanol, which became clear upon heating, was poured into a solution of hydroxylamine hydrochloride (690 mg, 10 mM) in 5 mL of methanol, and the resulting mixture was cooled to 0°C for 1h. The KOH/ HONH_2 solution was filtered, and the fresh filtrate was used for the hydroxamation reaction above.

The following (6.1 thru 6.17) are the spectra of compounds synthesized according to the hydroxamation reaction described above.

6.1 SYNTHESIS OF (Compound 102)

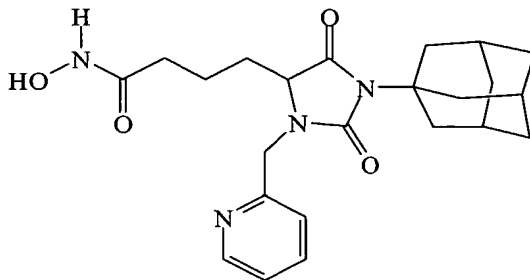


^1H NMR (360 MHz, $\text{DMSO}-d_6$): 1.23 (m_c , 1H, CH_2); 1.31 (m_c , 1H, CH_2); 1.66 (m_c , 8H), 1.83 (bt, 2H), 2.05 (bs, 3H), 2.33 (bd, 6H) (Ada-H, CH_2); 3.75 (t, $J = 4$ Hz, 1H, CH); 4.20, 4.64

(AA'BB', J ~15 Hz, 2H, NCH₂); 7.29 (m_c, 5H, Ar-H); 8.64, 10.28 (s, ~2H, CONHOH).

MS: m/e 426 (M⁺ + 1).

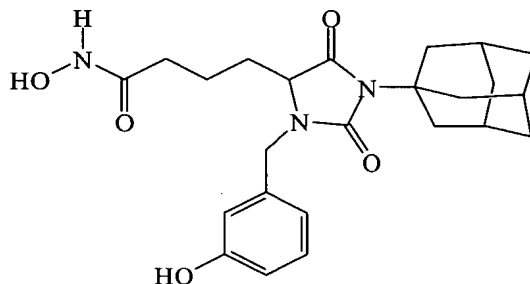
6.2 SYNTHESIS OF (Compound 174)



¹H NMR (360 MHz, DMSO-d₆): 1.26 (m_c, 1H, CH₂); 1.40 (m_c, 1H, CH₂); 1.65 (m_c, 8H), 1.86 (bt, 2H), 2.05 (bs, 3H), 2.33 (bd, 6H) (Ada-H, CH₂); 3.95 (t, J = 4 Hz, 1H, CH); 4.31, 4.72 (AA'BB', J = 16 Hz, 2H, NCH₂); 7.28 (m_c, 2H), 7.76 (m_c, 1H), 8.49 (d, J = 5 Hz, 1H) (Ar-H); 8.62, 10.28 (s, ~2H, CONHOH).

MS: m/e 427 (M⁺ + 1).

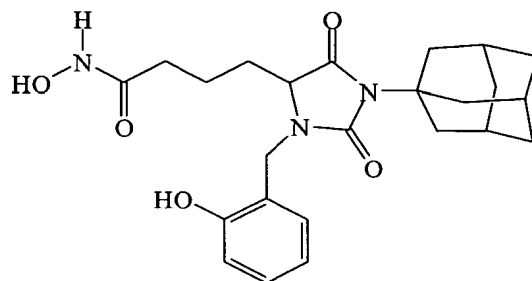
6.3 SYNTHESIS OF (Compound 161)



¹H NMR (360 MHz, DMSO-d₆): 1.23 (m_c, 1H, CH₂); 1.32 (m_c, 1H, CH₂); 1.67 (m_c, 8H), 1.86 (bt, 2H), 2.06 (bs, 3H), 2.34 (bd, 6H) (Ada-H, CH₂); 3.71 (t, J = 4 Hz, 1H, CH); 4.06, 4.60 (AA'BB', J ~14 Hz, 2H, NCH₂); 6.65 (m_c, 3H), 7.14 (t, J = .8 Hz, 1H) (Ar-H); 8.64, 9.39, 10.29 (s, ~3H, CONHOH, OH).

MS: m/e 442 (M⁺ + 1).

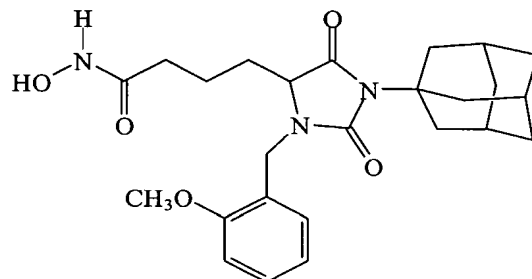
6.4 SYNTHESIS OF (Compound 155)



¹H NMR (360 MHz, DMSO-d₆): 1.24 (m_c, 1H, CH₂); 1.39 (m_c, 1H, CH₂); 1.64 (m_c, 8H), 1.86 (bt, 2H), 2.05 (bs, 3H), 2.33 (bd, 6 H) (Ada-H, CH₂); 3.70 (t, J = 4 Hz, 1H, CH); 4.10, 4.60 (AA'BB', J ~15 Hz, 2H, NCH₂); 6.77 (m_c, 2H), 7.10 (m_c, 2H) (Ar-H); 8.63, 9.58, 10.28 (s, ~3H, CONHOH, OH).

MS: m/e 442 (M⁺ + 1).

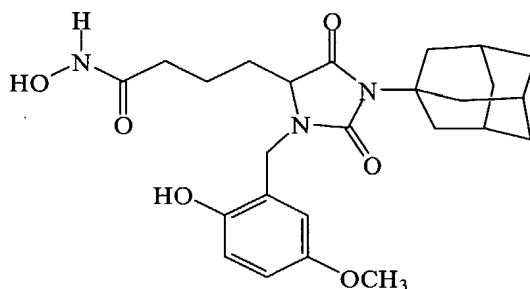
6.5 SYNTHESIS OF (Compound 163)



¹H NMR (360 MHz, DMSO-d₆): 1.26 (m_c, 1H, CH₂); 1.39 (m_c, 1H, CH₂); 1.65 (m_c, 8H), 1.88 (bt, 2H), 2.06 (bs, 3H), 2.34 (bd, 6 H) (Ada-H, CH₂); 3.68 (t, J = 4 Hz, 1H, CH); 3.79 (s, 3H, CH₃); 4.16, 4.62 (AA'BB', J ~15 Hz, 2H, NCH₂); 6.92 (m_c, 1H), 7.00 (d, 1H), 7.18 (dd, 1H), 7.28 (m_c, 1H) (Ar-H); 8.64, 10.30 (s, ~2H, CONHOH).

MS: m/e 456 (M⁺ + 1).

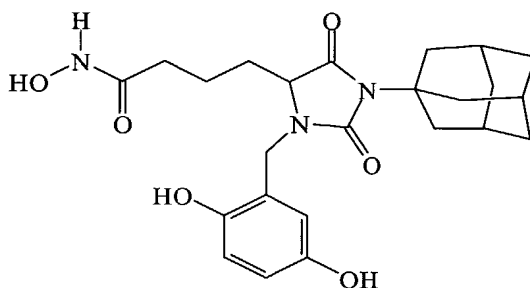
6.6 SYNTHESIS OF (Compound 139)



¹H NMR (360 MHz, DMSO-d₆): 1.24 (m_c, 1H, CH₂); 1.38 (m_c, 1H, CH₂); 1.64 (m_c, 8H), 1.87 (bt, 2H), 2.05 (bs, 3H), 2.33 (bd, 6H) (Ada-H, CH₂); 3.63 (s, 3H, CH₃); 3.71 (t, J ~ 4 Hz, 1H, CH); 4.10, 4.55 (AA'BB', J ~ 15 Hz, 2H, NCH₂); 6.68 (m_c, 3H, Ar-H); 8.64, 9.11, 10.29 (s, ~3H, CONHOH, OH).

MS: m/e 472 (M⁺ + 1).

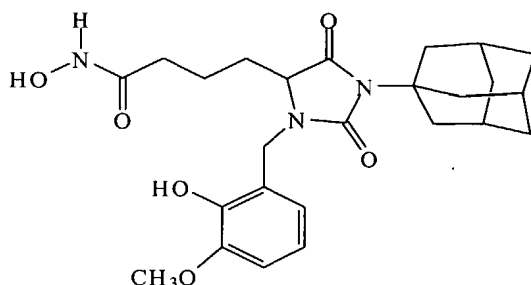
6.7 SYNTHESIS OF (Compound 137)



¹H NMR (360 MHz, DMSO-d₆): 1.23 (m_c, 1H, CH₂); 1.38 (m_c, 1H, CH₂); 1.64 (m_c, 8H), 1.88 (bt, 2H), 2.05 (bs, 3H), 2.33 (bd, 6H) (Ada-H, CH₂); 3.70 (t, J ~ 4 Hz, 1H, CH); 4.04, 4.50 (AA'BB', J ~ 15 Hz, 2H, NCH₂); 6.48, 6.62 (m_c, 3H, Ar-H); 8.66, 8.84, 10.29 (s, ~4H, CONHOH, OH).

MS: m/e 458 (M⁺ + 1).

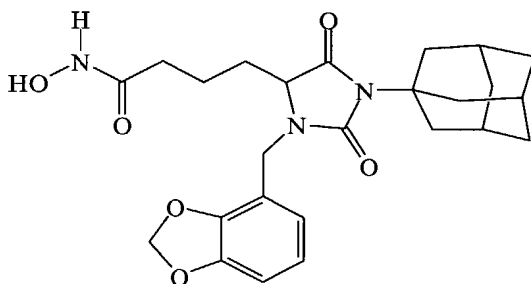
6.8 SYNTHESIS OF (Compound 168)



¹H NMR (360 MHz, DMSO-d₆): 1.20 (m_c, 1H, CH₂); 1.38 (m_c, 1H, CH₂); 1.65 (m_c, 8H), 1.88 (bt, 2H), 2.06 (bs, 3H), 2.33 (bd, 6 H) (Ada-H, CH₂); 3.69 (t, J ~4 Hz, 1H, CH); 3.78 (s, 3H, CH₃); 4.15, 4.61 (AA'BB', J ~15 Hz, 2H, NCH₂); 6.73, 6.90 (m_c, 3H, Ar-H); 8.64, 8.77, 10.29 (s, ~3H, CONHOH, OH).

MS: m/e 472 (M⁺ + 1).

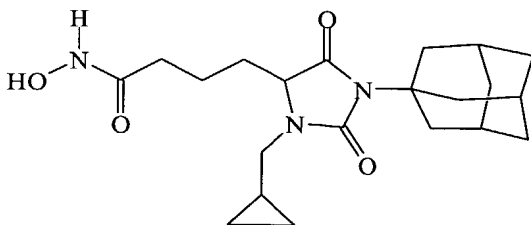
6.9 SYNTHESIS OF (Compound 179)



¹H NMR (360 MHz, DMSO-d₆): 1.23 (m_c, 1H, CH₂); 1.37 (m_c, 1H, CH₂); 1.64 (m_c, 8H), 1.85 (bt, 2H), 2.05 (bs, 3H), 2.32 (bd, 6 H) (Ada-H, CH₂); 3.77 (t, J ~4 Hz, 1H, CH); 4.15, 4.61 (AA'BB', J ~15 Hz, 2H, NCH₂); 6.00 (s, 2H, OCH₂); 6.78 (m_c, 3H, Ar-H); 8.63, 10.29 (s, ~2H, CONHOH).

MS: m/e 470 (M⁺ + 1).

6.10 SYNTHESIS OF (Compound 131)

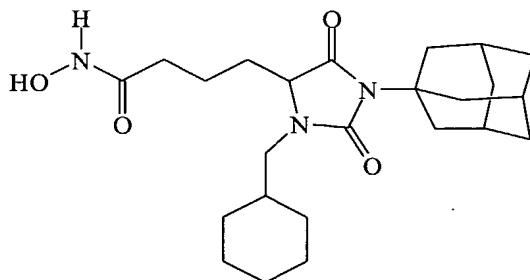


¹H NMR (360 MHz, DMSO-d₆): 0.23, 0.47 (m_c, 4H, CH₂); 0.94, 1.25, 1.45 (m_c, 3H), 1.79 (m_c, 8H), 1.92 (t, 2H), 1.96 (bs, 3H), 3.33

(bd, 6H) (Ada-H, CH, CH₂); 2.88, 3.27 (dd, J = 7 Hz and 14 Hz, 2H, CH₂); 4.03 (t, J = 4 Hz, 1H, CH); 8.64, 10.31 (s, ~2H, CONHOH).

5 MS: m/e 390 (M⁺ + 1).

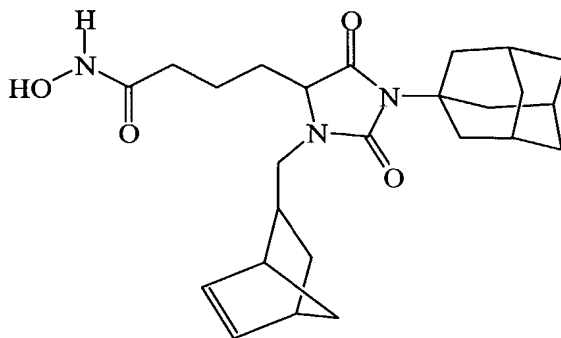
6.11 SYNTHESIS OF (Compound 127)



¹H NMR (360 MHz, DMSO-d₆): 0.86, 1.22, 1.63 (m_c, 21H); 1.92 (t, 2H), 2.03 (bs, 3H), 2.30 (bd, 6H) (Ada-H, CH, CH₂); 2.78, 3.26 (bdd, 2H, NCH₂); 3.93 (t, J = 4 Hz, 1H, CH); 8.65, 10.31 (s, ~2H, CONHOH).

15 MS: m/e 432 (M⁺ + 1).

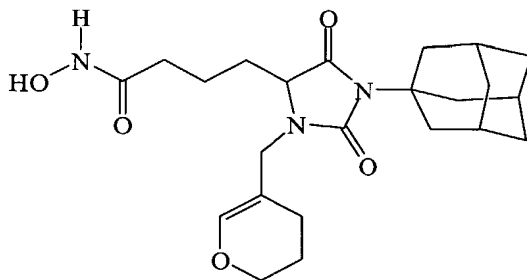
6.12 SYNTHESIS OF (Compound 128)



¹H NMR (360 MHz, DMSO-d₆): 1.30, 1.69 (m_c, 13H); 1.94 (bt, 2H), 2.06 (bs, 3H), 2.31 (m_c, 6H), 2.70 (m_c, 3H), 3.11 (m_c, 1H) (Ada-H, CH, CH₂); 3.98, 4.03 (t, J ~ 4Hz, 1H, CH); 6.03, 6.19 (m_c, 2H, =CH); 8.64, 10.31 (s, ~2H, CONHOH).

25 MS: m/e 442 (M⁺ + 1).

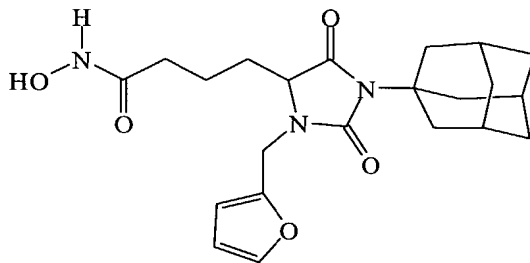
6.13 SYNTHESIS OF (Compound 192)



¹H NMR (360 MHz, DMSO-d₆): 1.26, 1.36 (m_c, 2H, CH₂); 1.64, 1.76
36 (m_c, 12H), 1.92 (bt, 2H), 2.04 (bs, 3H), 2.31 (bd, 6H)
(Ada-H, CH, CH₂); 3.40 (d, J = 14 Hz, 1H), 3.76 (t, J ~4 Hz,
1H), 3.83 (bt, J ~4 Hz, 2H), 4.00 (d, J ~ 14 Hz, 1H) (NCH₂
, OCH₂, CH); 6.46 (s, 1H, =CH); 8.63, 10.31 (s, ~2H, CONHOH).

MS: m/e 432 (M⁺ + 1).

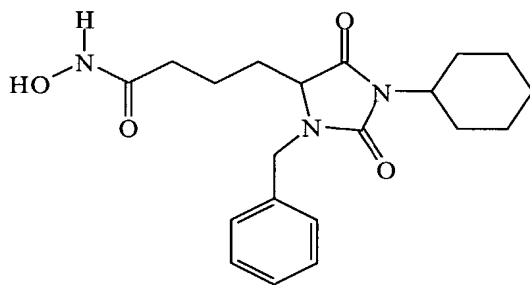
6.14 SYNTHESIS OF (Compound 176)



¹H NMR (360 MHz, DMSO-d₆): 1.25 (m_c, 2H, CH₂); 1.64 (m_c, 8H),
1.86 (bt, 2H), 2.05 (bs, 3H), 2.32 (bd, 6 H) (Ada-H, CH₂); 3.77
(t, J = 4 Hz, 1H, CH); 4.30, 4.56 (AA'BB', J ~16 Hz, 2H, NCH₂);
6.39, 7.59 (m_c, 3H, =CH); 8.63, 10.29 (s, ~2H, CONHOH).

MS: m/e 416 (M⁺ + 1).

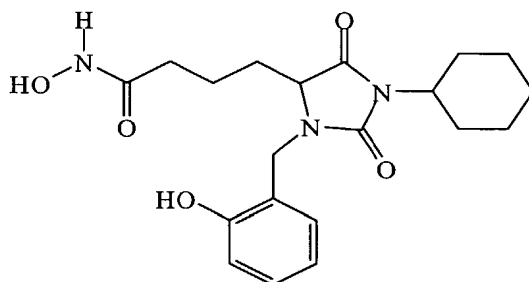
6.15 SYNTHESIS OF (Compound 107)



¹H NMR (360 MHz, DMSO-d₆): 1.29 (m_c, 5H), 1.68 (m_c, 9H), 2.01 (m_c, 2H) (H₂); 3.78 (m_c, 1H, NCH); 3.89 (t, J ~4 Hz, 1H, CH); 4.25, 4.68 (AA'BB', J ~15 Hz, 2H, NCH₂); 7.29 (m_c, 5H, Ar-H); 8.62, 10.27 (s, ~2H, CONHOH).

MS: m/e 374 (M⁺ + 1).

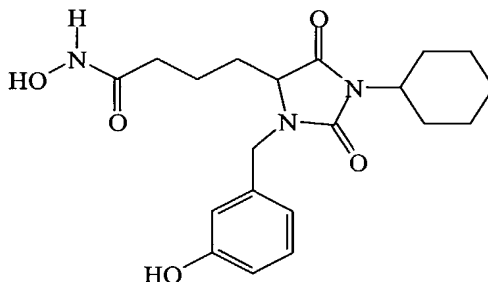
6.16 SYNTHESIS OF (Compound 195)



¹H NMR (360 MHz, DMSO-d₆): 1.28 (m_c, 5H), 1.58, 1.72, 1.87 (m_c, 9H), 2.01 (m_c, 2H) (CH₂); 3.79 (m_c, 2H, NCH, CH); 4.18, 4.64 (AA'BB', J ~ 15 Hz, 2H, NCH₂); 6.78, 7.11 (m_c, 4H, Ar-H); 8.63, 9.60, 10.29 (s, ~3H, CONHOH, OH).

MS: m/e 390 (M⁺ + 1).

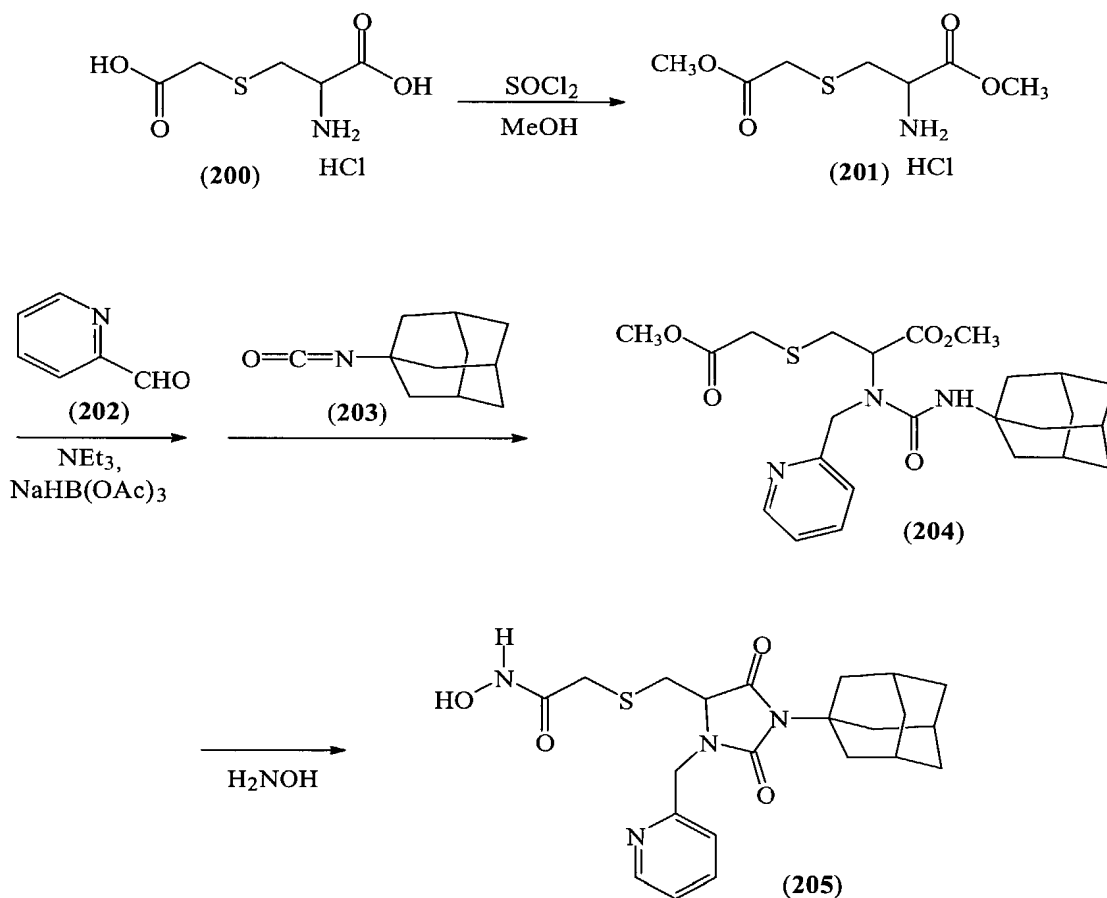
6.17 SYNTHESIS OF (Compound 198)



¹H NMR (360 MHz, DMSO-d₆): 1.25 (m_c, 5H), 1.72 (m_c, 9H), 2.05 (m_c, 2H) (CH₂); 3.79 (m_c, 1H, NCH); 3.86 (t, J ~4 Hz, 1H, CH); 4.13, 4.64 (AA'BB', J ~15 Hz, 2H, NCH₂); 6.68 (m_c, 3H), 7.13 (t, J ~8 Hz, 1H) (Ar-H); 8.62, 9.38, 10.28 (s, ~3H, CONHOH, OH).

MS: m/e 390 (M⁺ + 1).

6.18 SYNTHESIS OF (Compound 199)

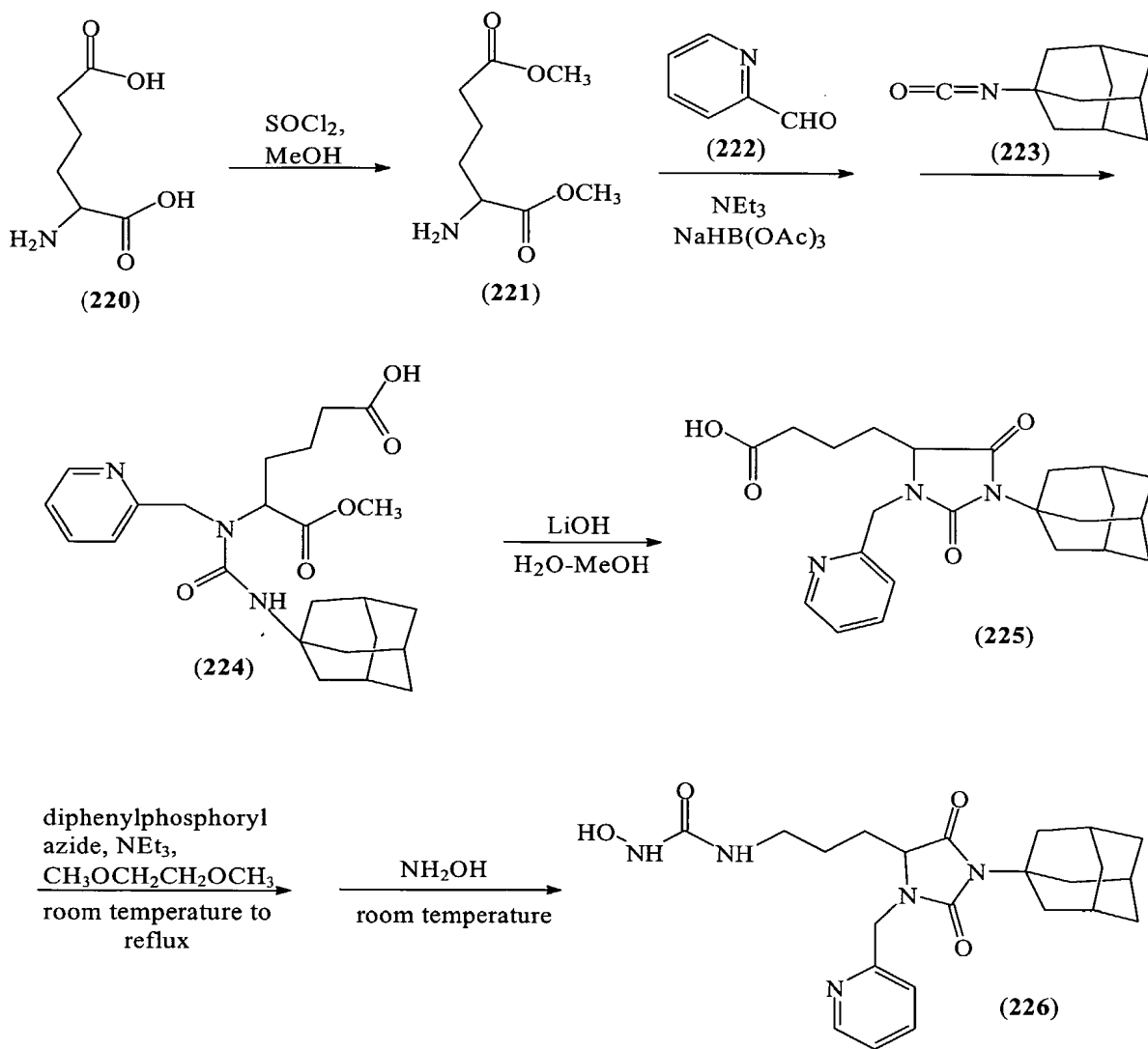


- 5 Compound **200** is commercially available (Aldrich).
 Compound **200** was mixed with SOCl_2 in MeOH to yield compound
201. To compound **201** (0.5 mM) in CH_2Cl_2 (5 mL) was added
 triethylamine (0.55 mM), aldehyde **202** (0.55 mM), and sodium
 triacetoxyborohydride (0.7 mM). The reaction mixture was
 10 shaken at room temperature for six hours, and then adamantyl
 isocyanate **203** (0.55 mM) was added. The mixture was shaken for
 an additional twelve hours and then quenched with 1 mL of 1 N
 HCl. The organic phase was washed with water (5 mL), dried
 over MgSO_4 , filtered, and concentrated to yield residue **204**.
 15 Residue **204** was treated with freshly prepared hydroxylamine
 solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched
 with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was

washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield title compound **205**. Title compound **205** is triturated in ether/hexane (1:1, 5 mL), and dried *in vacuo*.

5

6.19 SYNTHESIS OF (Compound 200)



10

D,L-2-amino-butanedioic acid **220** was mixed with SOCl_2 in MeOH to yield D,L-2-amino-butanedioic acid **221**. To compound **221** (0.5 mM) in CH_2Cl_2 (5 mL) was added triethylamine (0.55 mM), aldehyde **222** (0.55 mM), and sodium triacetoxymethylborohydride (0.7 mM). The reaction mixture was shaken at room temperature for six hours, and then admantylisocyanate **223** (0.55 mM) was added. The mixture was shaken for an additional twelve hours and then quenched with 1 mL of 1 N HCl. The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield residue **224**. Residue **224** was treated with LiOH to yield hydantoin **225**. Hydantoin **225** was mixed with diphenylphosphoryl azide, triethylamine, and ethylene glycol and refluxed at room temperature to form an isocyanate. The isocyanate was treated with freshly prepared hydroxylamine solution (1.5 mL, 1.5 mM) for twelve hours, and then quenched with 2 mL of 1N HCl, and 6 mL of CH_2Cl_2 . The organic phase was washed with water (5 mL), dried over MgSO_4 , filtered, and concentrated to yield title compound **226**.

6.20 SYNTHESIS OF OTHER COMPOUNDS

Other compounds of the invention can be synthesized by routine modification of the above-described syntheses, or by other methods that are well-known in the art. Appropriate starting materials are commercially available or can be synthesized using routine methods.

7. EXAMPLE: C-PROTEINASE IC_{50} ASSAYS

The following assay may be used to determine the level of activity and effect of the different compounds of the present invention on C-proteinase activity.

To determine inhibition of recombinant human C-proteinase, 60 μl of a reaction mix (final concentration in 100 μl of 0.05M Tris-HCl pH 7.6, 0.1M NaCl, 0.02% Brij-35, 5

mM CaCl₂ and 50 μ M of a fluorogenic peptide) was added to 20 μ l of the inhibitor in a 96 well plate. The reaction was started with the addition of 20 μ l of the recombinant human C-proteinase mix. The reaction proceeded for 4 hours at 37°C and the fluorescence was measured using a Bio-Tek Fl-600. The IC₅₀ was determined by plotting the percentage of activity versus the inhibitor concentration and estimating the inhibitor concentration that gives 50% activity of the control with no inhibitor.

The IC₅₀ values of exemplary inhibitors of the present invention are shown in Table 10.

TABLE 10
C-Proteinase Inhibitor IC₅₀ (μ M) Values

Compound #	IC ₅₀ (μ M)
102	0.77
174	0.21
161	0.14
155	0.27
163	0.60
139	0.26
137	0.059
168	0.43
179	0.23
131	0.43
127	0.29
128	0.40
192	0.21
176	0.23
107	3.33
195	1.08

198	1.24
193	22.93
194	18.99
199	0.29

5

7.2 TISSUE CULTURE ASSAY FOR THE DETERMINATION OF C-PROTEINASE ACTIVITY AND THE IC₅₀ OF INHIBITORS

10 C-proteinase activity and the IC₅₀ of inhibitors *in vivo*
may be determined in tissue culture assays by measuring the
production of procollagen and mature collagen in conditioned
medium before and after treatment with a particular compound.
The ratio of collagen and procollagen will directly correlate
15 to the cellular conversion of the precursor to the mature
collagen product, and as such indicates the C-proteinase
activity.

Alternatively, the media content of C-propeptide/cell may
be determined, and compared for untreated cells and
20 inhibitor-treated cells.

7.3 ANIMAL MODELS FOR THE DETERMINATION OF C-PROTEINASE ACTIVITY AND THE EFFICACY OF INHIBITORS

25 Several animal models which mimic clinical disorders
related to unregulated or inappropriate collagen production
are known in the art and may be employed to determine the *in*
vivo efficacy of the compounds of the invention. These animal
models include a wound chamber model in rats (Schilling et
30 al., 1959, *Surgery* 46:702-710), an estradiol stimulated uterus
expansion model (Mandell et al., 1982, *The Journal of*
Biological Chemistry 257:5268-5273), and an induced
angiogenesis model (Matrigel) (Passaniti et al., 1992,
Laboratory Investigation 67:519-528). Further animal models

include clinical disorder models like liver fibrosis models (Tsukamoto et al., 1990, *Seminar in Liver Disease* 10:56-65; Kock-Weser, 1952, *Laboratory Investigation* 1:324-331; Marrione, 1949, *American Journal of Pathology* 25:273-285; 5 Tams, 1957, *American Journal of Pathology* 33:13-27; Wahl et al., 1986, *Journal of Experimental Medicine* 163:884-902), a pulmonary fibrosis model (Kelly et al., 1980, *Journal of Laboratory Clinical Medicine* 96:954-964), arterial restenosis models (Jackson, 1994, *Trends of Cardiovascular Medicine* 10 4:122-130; Clowes et al., 1983, *Laboratory Investigation* 49:327-333), a kidney fibrosis model (Yamamoto et al., 1987, *Kidney International* 32:514-525), a tendon repairing model (Franklin et al., 1986, *The Journal of Laboratory and Clinical Medicine* 108:103-108), a tumor growth model (Kiohs, et al., 15 1985, *JNCL* 75:353-359), a trabeculectomy model (Lahery et al., 1989, *Journal of Ocular Pharmacology* 5:155-179), and an abdominal adhesions model (Williams et al., 1992, *Journal of Surgical Research* 52:65-70).

20 8.0 Conclusion

The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and any compounds and methods for the use thereof which are 25 functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the 30 scope of the appended claims.

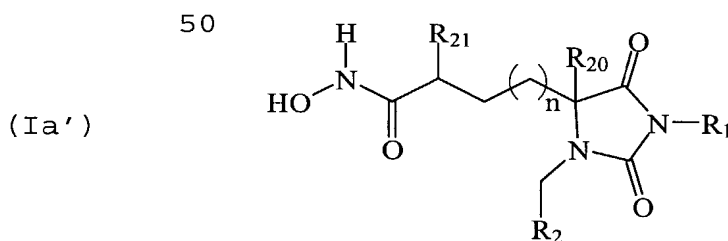
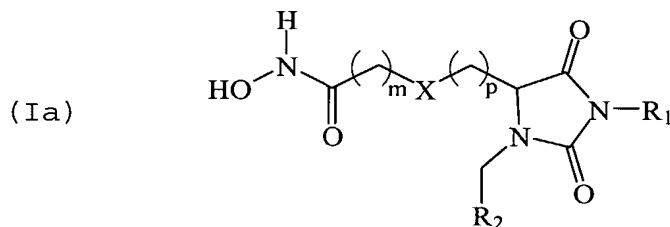
All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent

application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

CLAIMS

What Is Claimed:

1. A compound having the structural formulae:



or pharmaceutically acceptable salts thereof, wherein:

m is an integer from 0 to 3 when X is NR₁₉, or an integer from 1 to 3 when X is S or O;

p is an integer from 1 to 4 when X is NR₁₉, or an integer from 1 to 3 when X is S or O;

n is an integer from 1 to 3;

X is NR₁₉, S or O;

R₁₉ is selected from the group consisting of hydrogen, (C₁-C₅) alkyl, and (C₁-C₅) substituted alkyl;

R₁ and R₂ are each independently selected from the group consisting of (C₁-C₁₀) alkyl, (C₁-C₁₀) substituted alkyl, (C₃-C₁₀) alkenyl, (C₃-C₁₀) substituted alkenyl, (C₃-C₁₀) alkynyl, (C₃-C₁₀) substituted alkynyl, (C₃-C₂₀) cycloalkyl, (C₃-C₂₀) substituted cycloalkyl, 3-20 membered heterocycloalkyl, 3-20 membered substituted heterocycloalkyl, (C₅-C₂₀) aryl, (C₅-C₂₀) aryl independently substituted with one or more Y¹, alkaryl, alkaryl independently substituted with one or more Y¹, 5-20 membered heteroaryl, 5-20 membered heteroaryl independently substituted

with one or more Y^1 , 6-26 membered alk-heteroaryl, and 6-26 membered alk-heteroaryl independently substituted with one or more Y^1 ;

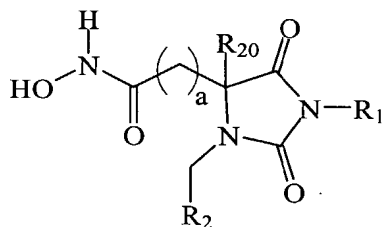
R_{20} and R_{21} are each independently selected from the group consisting of hydrogen, (C_1-C_{10}) alkyl, (C_6-C_{26}) alkaryl, and 6-26 membered alk-heteroaryl; and

each Y^1 is independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR,

-C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃ and -heteroaryl; where each R is independently selected from the group consisting of hydrogen, (C_1-C_8) alkyl, (C_3-C_8) alkenyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 6-20 membered heteroaryl and 6-26-membered alk-heteroaryl;

with the proviso that the sum of **m** and **p** is 1, 2, 3 or 4.

2. The compound of Claim 1 having the structural formula:

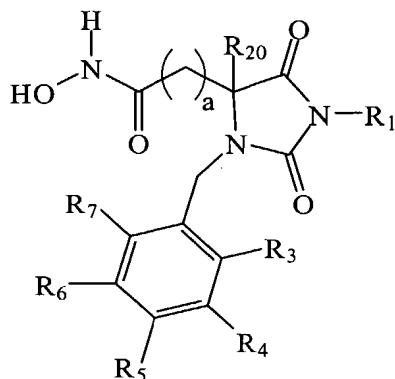


or pharmaceutically acceptable salts thereof, wherein:

a is an integer from 2 to 5; and

R_1 , R_2 , and R_{20} are as defined in Claim 1.

3. The compound of Claim 2 having the structural formula:

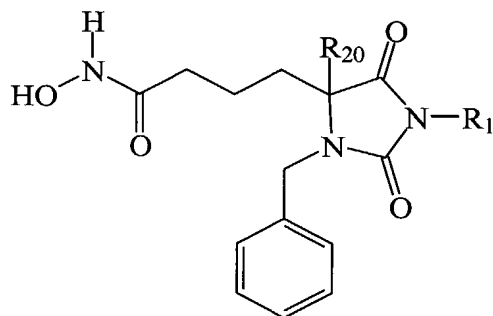


or pharmaceutically acceptable salts thereof, wherein:

a, R_1 , and R_{20} are as defined as in Claim 2; and

5 R_3 , R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of, -hydrogen, -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, 10 -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃ and -tetrazole; where each R is independently selected from the group consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered 15 heteroaryl and 6-26-membered alk-heteroaryl.

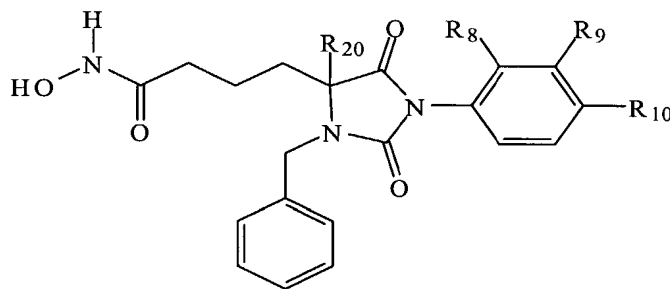
4. The compound of Claim 3 having the structural formula:



20 or pharmaceutically acceptable salts thereof, wherein R_1 is as defined in Claim 3.

5. The compound of Claim 4 selected from the group consisting of compound 101, compound 102, compound 103, compound 104, 105, compound 106, compound 107, compound 108, and compound 109.

6. The compound of Claim 2 having the structural formula:



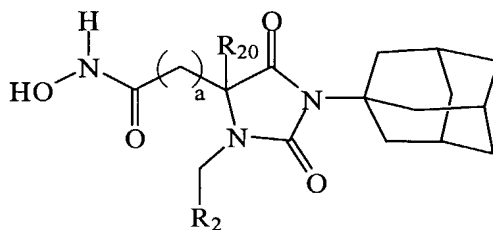
or pharmaceutically acceptable salts thereof, wherein:

R_8 , R_9 and R_{10} are each independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃ and -tetrazole; where each R is independently selected from the group consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₃-C₈) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl and 6-26-membered alk-heteroaryl; and

R_{20} is as defined as in Claim 2.

7. The compound of Claim 6 selected from the group consisting of compound 110, compound 111, compound 112, compound 113, compound 114, compound 115, compound 116, compound 117, compound 118, compound 119, compound 120, compound 121, compound 122, compound 123, compound 124, and compound 125.

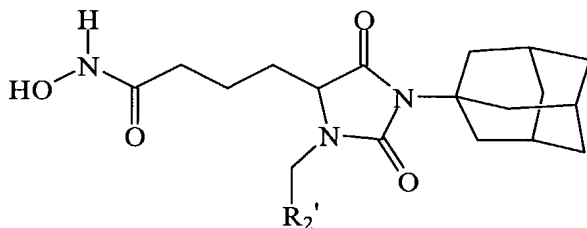
8. The compound of Claim 2 having the structural formula:



5 or pharmaceutically acceptable salts thereof, wherein a , R_2 , and R_{20} are as defined as in Claim 2.

9. The compound of Claim 8 having the structural formula:

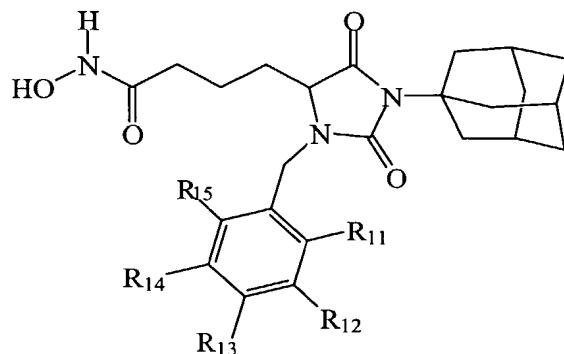
10



or pharmaceutically acceptable salts thereof, wherein R_2' is selected from the group consisting of (C_1-C_{10}) alkyl, (C_1-C_{10}) substituted alkyl, (C_3-C_{10}) alkenyl, (C_3-C_{10}) substituted alkenyl, (C_3-C_{10}) alkynyl, (C_3-C_{10}) substituted alkynyl, (C_3-C_{20}) cycloalkyl, (C_3-C_{20}) substituted cycloalkyl, (C_5-C_{20}) aryl, (C_5-C_{20}) aryl independently substituted with one or more Y^1 , alkaryl, alkaryl independently substituted with one or more Y^1 ; and Y^1 are as defined in Claim 2.

20 10. The compound of Claim 9 selected from the group consisting of compound 126, compound 127, compound 128, compound 129, compound 130, compound 131, compound 132, compound 133, and compound 134.

25 11. The compound of Claim 8 having the structural formula:

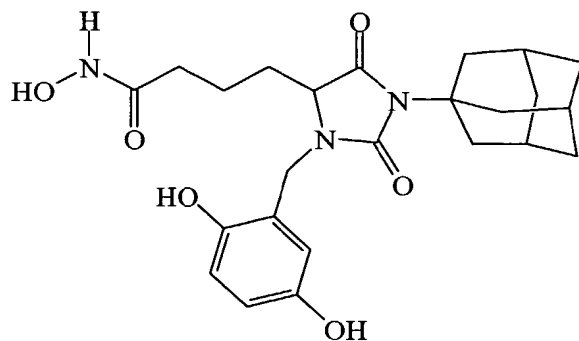


or pharmaceutically acceptable salts thereof, wherein:

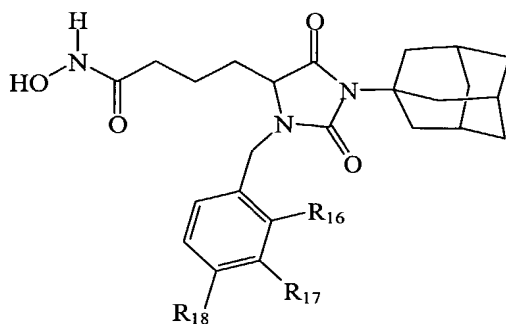
R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} is each independently selected from the group consisting of -halogen, -trihalomethyl, -R, -C(O)OR, -CN, -C(O)-NR-OR, -C(NRR)=N-OR, -C(O)-R, -C(O)NRR, -C(S)NRR, -C(NRR)=NR, -NRR, -NO₂, -N₃, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(O)-OR, -NR-SO₂-R, -NR-C(S)-NRR, -NR-C(O)R, -NR-C(O)-NRR, -NR-C(S)-NRR, -OR, -P(O)(OH)(NRR), -P(O)(OH)₂, -SO₂R, -S(O)-R, -SO₃H, -SR, -SO₂-NRR, -OCF₃ and -tetrazole; where each R is independently selected from the group consisting of -H, (C₁-C₈) alkyl, (C₃-C₈) alkenyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 6-20 membered heteroaryl and 6-26-membered alk-heteroaryl.

12. The compound of Claim 11 selected from the group consisting of compound 135, compound 136, compound 137, compound 138, compound 139, compound 140, compound 141, compound 142, compound 143, compound 144, compound 145, and compound 146.

13. The compound of Claim 11 having the structural formula:



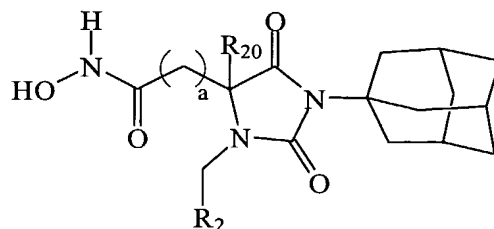
14. The compound of Claim 8 having the structural formula:



or pharmaceutically acceptable salts thereof, wherein R₁₄ and R₁₅ are hydrogen.

15. The compound of Claim 14 selected from the group consisting of compound 102, compound 148, compound 149, compound 150, compound 151, compound 152, compound 153, compound 154, compound 155, compound 156, compound 157, compound 158, compound 159, compound 160, compound 161, compound 162, compound 163, compound 164, compound 165, compound 166, compound 167, compound 168, compound 169, compound 170, compound 171, compound 172, and compound 173.

16. The compound of Claim 8 having the structural formula:



or pharmaceutically acceptable salts thereof, wherein:

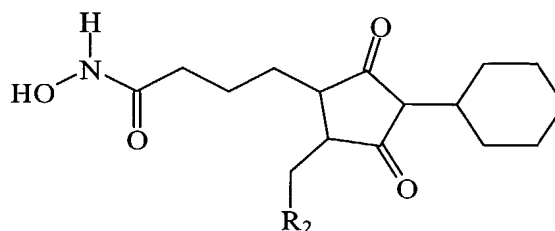
a, R_{20} , and Y^1 are as defined in Claim 8; and

5 R_2 is 5-20 membered heteroaryl, 5-20 membered heteroaryl independently substituted with one or more Y^1 , 3-20 membered heterocycloalkyl, 3-20 membered substituted heterocycloalkyl, 6-26 membered alk-heteroaryl, and 6-26 membered alk-heteroaryl independently substituted with one or more Y^1 ; wherein Y^1 is as
10 defined in Claim 1.

17. The compound of Claim 16 wherein **a** is 3 or pharmaceutically acceptable salts thereof.

15 18. The compound of Claim 17 selected from the group consisting of compound 174, compound 175, compound 176, compound 177, compound 178, compound 179, compound 180, compound 181, compound 182, compound 183, compound 184, compound 185, compound 186, compound 187, compound 188,
20 compound 189, compound 190, compound 191, and compound 192.

19. The compound of Claim 2 having the structural formula:



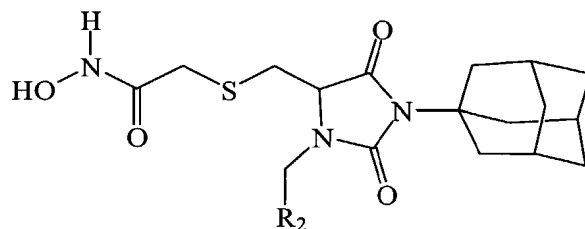
25 or pharmaceutically acceptable salts thereof, wherein R_2 is as defined as in Claim 2.

20. The compound of Claim 19 selected from the group consisting of compound 107, compound 194, compound 195, compound 196, compound 197, and compound 198.

5 21. The compound of Claim 1 wherein X is S or pharmaceutically acceptable salts thereof.

22. The compound of Claim 21 having the structural formula:

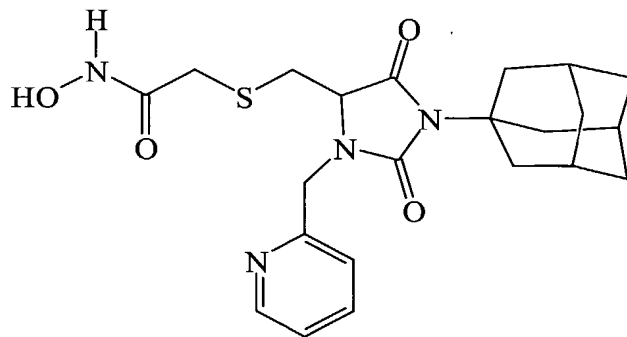
10



or pharmaceutically acceptable salts thereof, wherein R₂ is as defined in Claim 1.

15

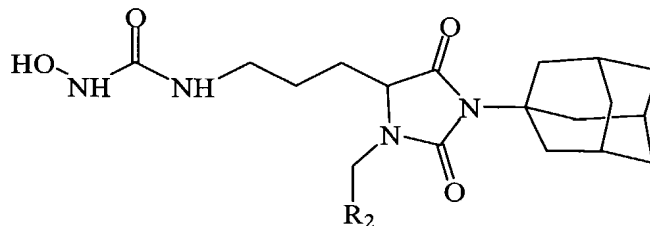
23. The compound of Claim 22 having the structural formula:



or pharmaceutically acceptable salts thereof.

24. The compound of Claim 1 wherein X is NR₁₉ or
20 pharmaceutically acceptable salts thereof.

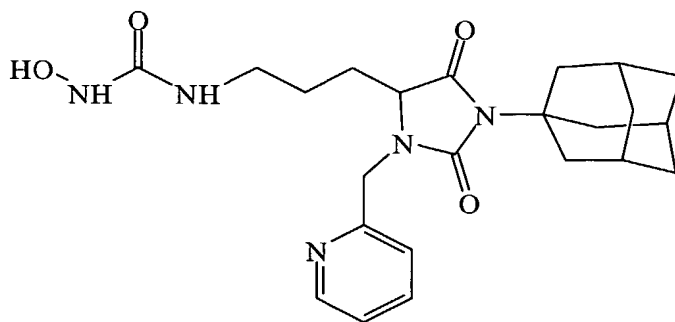
25. The compound of Claim 24 having the structural formula:



or pharmaceutically acceptable salts thereof, wherein R₂ is as defined in Claim 1.

5

26. The compound of Claim 25 having the structural formula:



or pharmaceutically acceptable salts thereof.

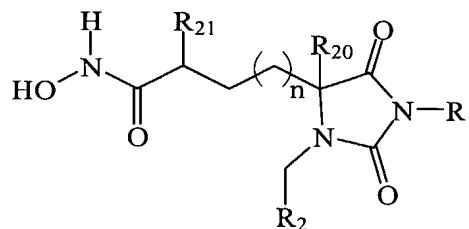
10

27. The compound of Claim 1 wherein X is O or pharmaceutically acceptable salts thereof.

28. The compound of Claim 1 having the structural formula:

15

50



or pharmaceutically acceptable salts thereof, wherein R₁, R₂, R₂₀, R₂₁ and n are as defined in Claim 1.

20

29. The compound of Claim 28 selected from the group consisting of compound H1, compound H2, compound H3, compound

H4, compound H5, compound H6, compound H7, compound H8,
compound H9, compound H10, compound H11, compound H12,
compound H13, compound H14, compound H15, compound H16,
compound H17, compound H18, compound H19, compound H20,
5 compound H21, compound H22, compound H23, compound H24, and
compound H25.

30. A pharmaceutical composition comprising the compound of
Claim 1 and a pharmaceutically acceptable carrier, diluent or
10 excipient.

31. A method of treating a disease related to inappropriate
or unregulated production of collagen, said method comprising
the step of administering to a subject in need thereof an
15 effective amount of a compound according to Claim 1.

32. A method of treating a fibrotic disorder selected from
the group consisting of hepatic cirrhosis and arthritis, said
method comprising the step of administering to a subject in
20 need thereof an effective amount of a compound according to
Claim 1.

INTERNATIONAL SEARCH REPORT

In: Application No
PCT/US 01/03410

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/78 A61P1/16 A61K31/415 C07D409/06 C07D405/06
C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 33709 A (HOFFMANN LA ROCHE ;BROADHURST MICHAEL JOHN (GB); BROWN PAUL ANTHON) 14 December 1995 (1995-12-14) page 13, paragraph 3; claim 5 -----	1-32
A	EP 0 640 594 A (FUJIREBIO KK) 1 March 1995 (1995-03-01) page 1, line 10 - line 18; claim 1 -----	1-32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 May 2001

Date of mailing of the international search report

07-06-01

Name and mailing address of the ISA

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Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/03410

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31 and 32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int | Application No

PCT/US 01/03410

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9533709 A	14-12-1995	AU 2735995 A EP 0763013 A JP 10500965 T US 6066662 A	04-01-1996 19-03-1997 27-01-1998 23-05-2000
EP 0640594 A	01-03-1995	JP 7126258 A	16-05-1995